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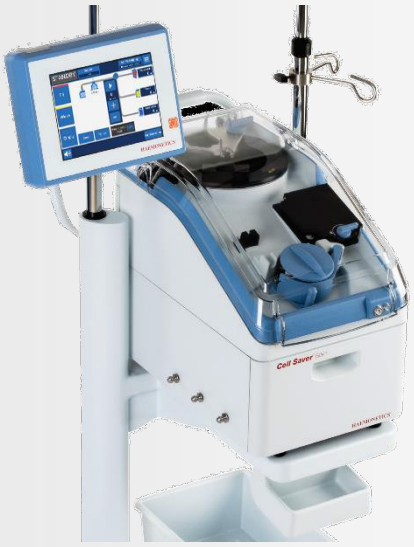

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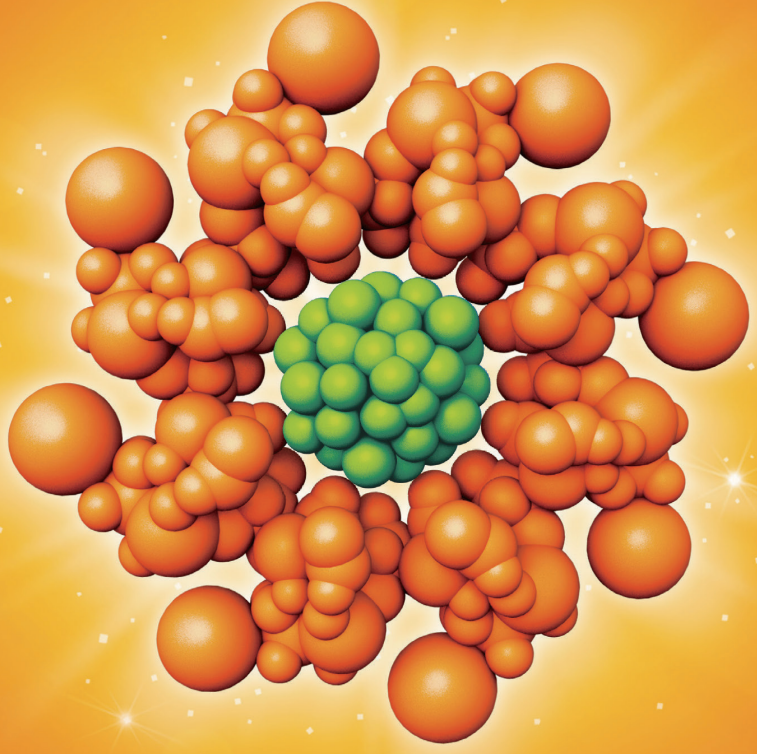

* 2 years and older † **Primary endpoint result :** A TOF ratio of 0.9 or higher was attained in a median time of less than 2 min with a sugammadex dose of 2.0 mg/kg in all age groups. infants(0.6), children(1.2), adolescents(1.1), adults(1.2).[2]

Study design a. The aim of this multicenter, randomized, parallel-group, dose-finding, safety-assessor blinded study was to explore the dose-response relationship of sugammadex given at reappearance of the second twitch (T_2) of the TOF stimulation for the reversal of rocuronium-induced neuromuscular blockade in infants, children, adolescents, and adults between May 2005 and May 2006. A total of 94 patients were randomized to receive sugammadex or placebo, of which 91 patients (8 infants, 24 children, 31 adolescents, and 28 adults) received the study medication (all-subjects-treated group). Anesthetized patients (American Society of Anesthesiologists class 1–2) received 0.6 mg/kg rocuronium and were randomized to receive sugammadex (0.5, 1.0, 2.0, or 4.0 mg/kg) or placebo at reappearance of T_2. Neuromuscular monitoring was performed using acceleromyography. Primary endpoint was time from sugammadex/placebo administration to recovery of the train-of-four ratio to 0.9.[2]

References : 1. BRIDION® Prescribing Information, MFDS. **2.** Plaud B, *et al*. Reversal of rocuronium-induced neuromuscular blockade with sugammadex in pediatric and adult surgical patients. *Anesthesiology*. 2009 Feb;110(2):284-94.

Bridion®(Sugammadex) 100 mg Selected Safety Information

[Indications and Usage] Reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults and pediatric patients aged ≥2 years old undergoing surgery. **[Dosage and Administration] Adult Patients:** Routine reversal: A dose of 4 mg/kg Bridion is recommended as IV injection if recovery has reached at least 1–2 post-tetanic counts(PTC) following rocuronium or vecuronium induced blockade. A dose of 2 mg/kg Bridion is recommended as IV injection, if spontaneous recovery has occurred up to at least the reappearance of T_2 following rocuronium or vecuronium induced blockade. **Immediate Reversal of Rocuronium-Induced Blockade:** A dose of 16 mg/kg Bridion is recommended if there is a clinical need to reversal neuromuscular blockade soon(approximately 3 minutes) after administration of rocuronium as IV injection. The safety and efficacy with the use of Bridion for immediate reversal following vecuronium induced blockade has not been established. **Renal Impairment:** No dosage adjustment is necessary for patients with mild or moderate renal impairment(creatinine clearance ≥30 mL/min and <80 mL/min). Bridion is not recommended for use in patients with severe renal impairment(creatinine clearance <30 mL/min) or dialysis. **Elderly Patients:** Elderly patients tend to delay recovery from neuromuscular blockade, but dose adjustment is not necessary. **Obese Patients:** The dose of this drug in obese patients should be based on actual weight(ABW). **Hepatic Impairment:** No dosage adjustment is necessary for patients with mild and moderate hepatic impairment. Since no clinical studies have been conducted with patients with hepatic impairment, caution should be taken in patients with severe hepatic impairment or hepatic impairment with coagulation disorders. **Pediatric Patients (≥2 years old):** Bridion 100 mg/mL may be diluted to a concentration of 10 mg/mL to increase the accuracy of dosing in the pediatric population. Routine Reversal: A dose of 4 mg/kg Bridion is recommended if spontaneous recovery of the twitch response has reached 1 to 2 post-tetanic counts(PTC) following rocuronium- or vecuronium-induced neuromuscular blockade. A dose of 2 mg/kg Bridion is recommended if spontaneous recovery has reached the reappearance of the second twitch(T_2) in response to TOF stimulation following rocuronium- or vecuronium-induced neuromuscular blockade. Immediate Reversal: Immediate reversal in pediatric patients has not been studied. Preparation of dilution for pediatric use: To prepare the required dose, aseptically transfer all the contents of the 2 mL vial of Bridion 2 mL single-dose vials containing 200 mg Bridion(100 mg/mL) to a bottle(or intravenous bag) containing 18 mL of 0.9% sodium chloride injection, to achieve a final concentration of 10 mg/mL Bridion. **[Warnings and Precautions] Contraindications:** Patients with known hypersensitivity to Bridion or any of its components. **Careful Administration:** 1) Patients with renal impairment 2) Patients with hepatic impairment 3) Patients with decrease of cardiac output 4) Patients with edema state 5) Patients with a history of allergic reaction 6) Patients with a history of pulmonary complications(Possible occurrence of bronchospasm) 7) Patients with coagulation disorders 8) Patients with arrhythmia 9) The elderly 10) Pregnant or women who may be pregnant. **Adverse Reactions:** 1) The safety of Bridion has been evaluated based on an integrated safety database of approximately 1,700 surgical patients and 120 healthy adult volunteers. The most commonly reported adverse reactions in patients who experienced surgery were anaesthetic complications. **Immune System:** 1) Hypersensitivity(≥1/1,000, <1/100), the others: Anaesthetic complications(body movement in the middle of anesthesia or operation, coughing, grimacing and sucking of the tracheal tube)(≥1/100, <1/10), unintended intraoperative awareness(≥1/1,000, <1/100). 2) In clinical trials with surgical patients, hypersensitivity including anaphylaxis has been reported infrequently. The frequency of occurrence of hypersensitivity reactions in post-marketing surveys is unknown. Hypersensitivity reactions that occurred varied from isolated skin reactions to serious systemic reactions(i.e., anaphylaxis, anaphylactic shock) and have occurred in patients with no prior exposure to Bridion. Symptoms associated with these reactions can include: flushing, urticaria, erythematous rash, severe hypotension, tachycardia, swelling of tongue, swelling of pharynx, bronchospasm and pulmonary obstructive events. Severe hypersensitivity reactions can be fatal. Hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with Bridion in clinical study for healthy volunteers(150 subjects received 4 mg/kg, 148 received 16 mg/kg and 150 received placebo). The incidence of adjudicated hypersensitivity was 0.7%(n=1) and 4.7%(n=7) in Bridion 4 mg/kg and Bridion 16 mg/kg groups, respectively. There were no reports of anaphylaxis after placebo. 3) In a dedicated clinical study in healthy volunteers, dysgeusia, nausea and flushing were reported and showed a dose response relationship. 4) In a few patients receiving Bridion, unintended intraoperative awareness was reported. It cannot be determined whether this event was causally related to Bridion. 5) Cases of marked bradycardia, bradycardia with cardiac arrest, ventricular fibrillation and ventricular tachycardia have been observed within minutes after administration of Bridion. Patients should be closely monitored for hemodynamic changes during and after reversal of neuromuscular blockade. If cardiac disorders should occur, appropriate treatment should be instituted. 6) In one dedicated clinical trial and in post-marketing data, in patients with a history of pulmonary complications, bronchospasm was reported as a possibly related adverse event. 7) Post-marketing clinical trials of obese patients(BMI ≥40 kg/m²) showed that the adverse reaction profile was generally similar between patients who were administered actual body weight(ABW) and patients who were administered ideal body weight(IBW). 8) One trial of 331 patients who were assessed as ASA Class 3(Patients with severe systemic disease) or 4(Patients with severe systemic disease that is a constant threat to life) investigated the incidence of treatment-emergent arrhythmias(sinus bradycardia, sinus tachycardia, or other cardiac arrhythmias) after administration of Bridion. The incidence of treatment-emergent sinus bradycardia in patients receiving Bridion(2 mg/kg, 4 mg/kg, or 16 mg/kg) was generally similar to those in patients receiving neostigmine(50 ug/kg up to 5 mg maximum dose) + glycopyrrolate(10 ug/kg up to 1 mg maximum dose). Incidence of treatment-emergent sinus bradycardia was statistically significantly lower in Bridion treatment group(2 mg/kg) compared to neostigmine treatment group(p=0.026). Incidence of treatment-emergent sinus tachycardia was statistically significantly lower in Bridion treatment group(2 mg/kg, 4 mg/kg) compared to neostigmine treatment group(p=0.007, 0.036). 9) During post-marketing surveillance period of 6 years in 718 subjects for re-examination, AEs were reported in 26.60%(191/718 subjects, 281 events), regardless of causal relationship. Among those, serious AE was hypertensive crisis, pruritus, purpura, urticaria, urinary retention, atrial fibrillation, etc. and there was no serious AE that cannot rule out relationship to Bridion. **General Cautions:** 1) Ventilatory support is mandatory for patients until adequate spontaneous respiration is restored following reversal of neuromuscular blockade. 2) In order to prevent recurrence of neuromuscular blockade, the recommended doses for routine should be used. 3) When drugs which potentiate neuromuscular blockade are used in the post-operative phase, special attention should be paid to the possibility of recurrence of neuromuscular blockade. 4) Recurrence of neuromuscular blockade may occur due to displacement of rocuronium or vecuronium from Bridion by other drugs(i.e., Toremifene, fusidic acid). 5) When neuromuscular blockade was reversed intentionally in the middle of anaesthesia in clinical trials, signs of light anaesthesia were noted occasionally(movement, coughing, grimacing and sucking of the tracheal tube). 6) In patients for whom intubation is expected to be difficult, the method of airway maintenance should be considered beforehand. If rocuronium-induced neuromuscular blockade cannot or does not allow airway intubation, it should be promptly restored from neuromuscular blockade. 7) Coagulation parameters should be carefully monitored in patients with known coagulopathies when Bridion is administered. 8) In patients with severe renal failure(creatinine clearance <30 mL/min), the excretion of Bridion or the Bridion-rocuronium complex was delayed; however, in these patients there were no signs of re-occurrence of neuromuscular blockade. This drug is not recommended for use in patients with severe renal impairment. 9) Dedicated studies in patients with hepatic impairment have not been conducted. Patients with severe hepatic impairment or hepatic impairment with coagulation disorders should be cautious when administering this drug. 10) Bridion has not been studied for reversal following rocuronium or vecuronium administration in the ICU. 11) Do not use Bridion to reverse neuromuscular blockade induced by nonsteroidal neuromuscular blocking agents such as succinylcholine or benzylisoquinolinium compounds, steroidal neuromuscular blocking agents, pancuronium other than rocuronium or vecuronium. 12) Conditions associated with prolonged circulation time such as cardiovascular disease, old age or edema state(i.e., severe hepatic impairment) may be associated with longer recovery times. 13) The patients should be carefully observed for the possibility of drug hypersensitivity reactions(including anaphylactic reactions). If any abnormality is observed, appropriate measures should be taken immediately. 14) Each 1 mL solution contains 9.7 mg sodium. If more than 2.4 mL(contain approximately 23 mg sodium) solution needs to be administered, this should be taken into consideration by patients on a controlled sodium diet. 15) In rare instances, cases of marked bradycardia, some of which have resulted in cardiac arrest, have been observed within minutes after the administration of Bridion for reversal of neuromuscular blockade. **Drug Interactions :** 1) Toremifene: For toremifene, which has a relatively high binding affinity for Bridion and for which relatively high plasma concentrations might be present, some displacement of vecuronium or rocuronium from the complex with this drug could occur. 2) Fusidic acid: IV administration of fusidic acid in the pre-operative phase may give some delay in the recovery of the T_4/T_1 ratio to 0.9. No recurrence of neuromuscular blockade is expected in the post-operative phase, since the infusion rate of fusidic acid is over a period of several hours and the blood levels are cumulative over 2–3 days. 3) Hormonal contraceptives: The interaction between 4 mg/kg Bridion and a progestogen was predicted to lead to a decrease in progestogen exposure(34% of AUC). **Pregnancy & Lactation Administration:** There are no clinical trial data for exposure to this drug during pregnancy. It is administered only if the benefits of administration exceed the risk. No data are available regarding the presence of Bridion in human milk, the effects of Bridion on the breast fed infant, or the effects of Bridion on milk production. Breastfeeding is not recommended during the administration of this drug. **Pediatric Administration:** In clinical study for pediatric patients 2 to <17 years of age, the safety profile of Bridion(4 mg/mg maximum dose) is generally consistent with that observed in adults. Safety and effectiveness in patients younger than 2 years of age have not been established. **Elderly Administration:** Exercise caution when administering Bridion to elderly patients who tend to delay recovery from neuromuscular blockade.(Revised: 2021.10.14)

※Before prescribing BRIDION, please refer to the full prescribing information for further details.

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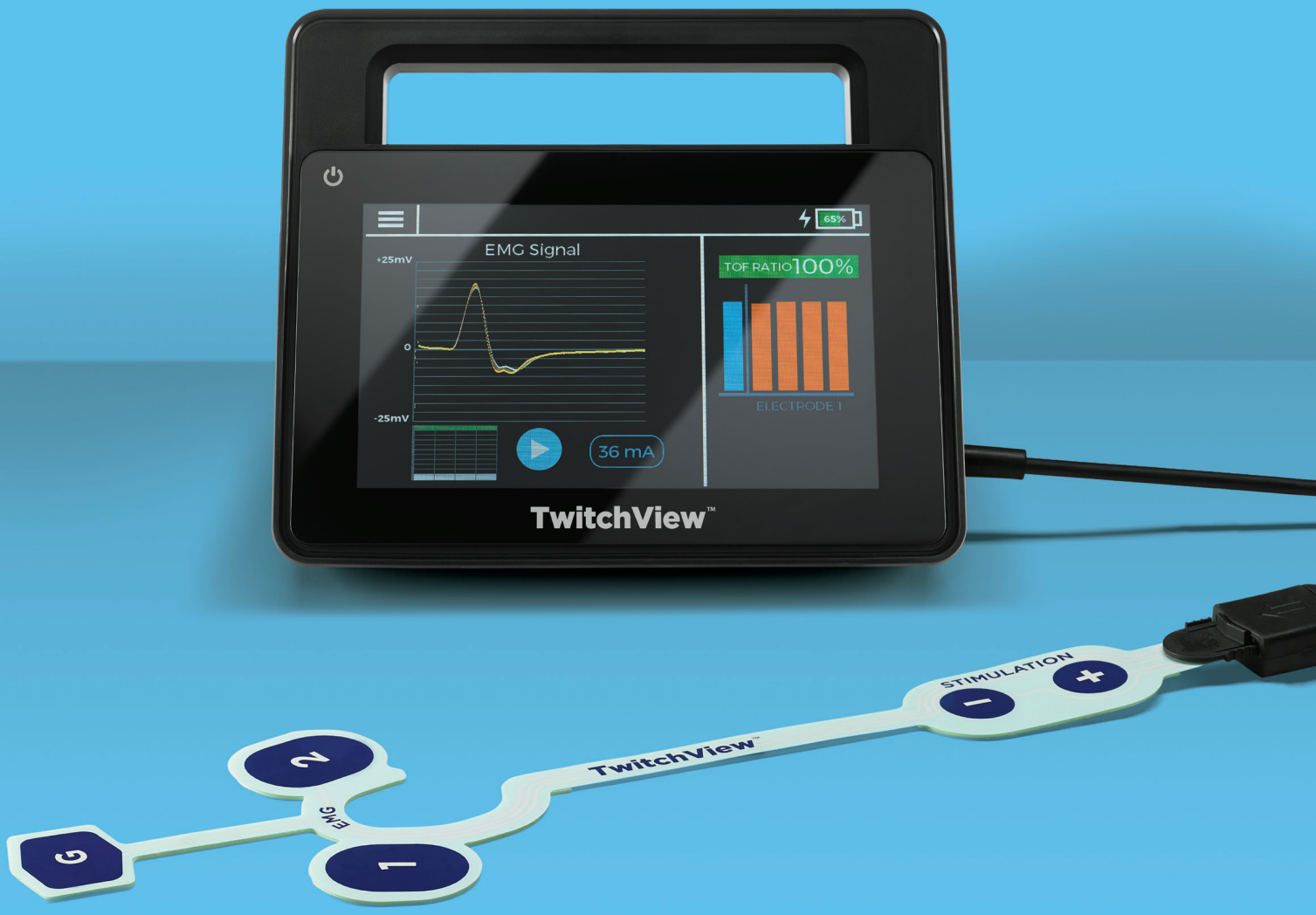

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Aims and Scope

The Korean Journal of Anesthesiology (Korean J Anesthesiol; KJA/ISSN: 2005-6419), an official journal of the Korean Society of Anesthesiologists, is an English-language, peer-reviewed journal that publishes articles in the fields of anesthesiology, critical care, and pain medicine. KJA aims to publish high-quality clinical and scientific materials on all aspects of anesthesiology, critical care, and pain medicine. Its regional focus is mainly Korea, but it also welcomes submissions from researchers all over the world.

In addition to publishing original articles, KJA features reviews, editorials, case reports, and letters to the editor. KJA also features statistical rounds to provide its readers with educational fundamentals and practical implications for clinical and experimental statistics. Additionally, KJA gladly publishes negative results, which will benefit clinical practice and promote further research activity.

The primary considerations for publication are clarity, uniqueness, and advancement in design, performance, and knowledge.

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Experimental Research Article

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Review Article

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Pediatric perioperative fluid management

소아 주술기 수액 관리

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소아에서 주술기 수액 관리의 목적은 주술기 동안 적절한 혈관내 용적, 전해질 농도 및 내분비계 항상성을 유지하기 위해서이다. 전통적으로 포도당이 포함된 저장액 용액이 소아에서 사용되어 왔지만, 최근의 연구에 따르면 등장성 균형 정질액이 주술기 저나트륨혈증 및 대사성 산증의 위험을 낮추는 것으로 보여진다. 등장성 균형 정질액은 주술기 수액 관리에 더 안전하고 생리적으로 적합한 특성을 나타내는 것으로 확인되었다. 또한, 지속 주입 수액에 1%–2.5%의 포도당을 추가하면 소아에서 저혈당 및 관련된 지질 동원, 케토시스, 고혈당을 예방하는 데 도움이 될 수 있다. 환자 안전을 위협하지 않는 범위에서 금식 시간은 가능한 한 짧아야 한다. 최근 가이드라인에서는 물의 경우 금식의 기간을 1시간으로 줄일 것을 권고하고 있다. 지속적인 체액 및 혈액 소실뿐만 아니라 항이뇨 호르몬 분비에 의해 유도되는 체액 저류는 수술 후 수액 관리 시 반드시 고려되어야 하는 독특한 특성이다. 등장성 균형 수액의 주입 속도를 줄이는 것은 수술 후 희석성 저나트륨혈증을 피하기 위해 필요할 수도 있다. 요약하면 소아 환자의 주술기 수액 관리는 성인보다 제한된 항상성 유지능력 때문에 세심한 주의가 필요하다. 등장성 균형 수액은 생리적 특성 및 안전 문제를 고려할 때 대부분의 소아 환자에게 가장 안전하고 유익한 선택으로 보인다.

Keywords: Anesthesia; Child; Fluid therapy; Infant; Intravenous infusion; Isotonic solutions; Perioperative medicine.

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Statistical Round

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Intention-to-treat versus as-treated versus per-protocol approaches to analysis

Intention-to-treat (ITT), as treated (AT) 및 per protocol (PP) 분석 접근법 비교

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무작위 대조 시험(randomized controlled trial, RCT)은 가설 검정을 위한 가장 엄격한 연구 설계이며, 중재 효과를 평가하기 위한 가장 효과적인 방법으로 알려져 있다. RCT는 일반적으로 이상적인 상황에 대한 가정하에서 수행되지만, 현실에서 실제 연구를 진행할 때는 참가자 등록 또는 중재 과정에서의 실수, 추적 관찰 동안의 누락 및 피험자들이 연구 계획을 잘 준수(compliance) 또는 이행(adherence)하지 않는 것과 같은 이상적인 상황과 다른 다양한 문제들이 수반된다. RCT 데이터 분석을 하기 위해서, 다양한 분석군 규정 전략들(group-defining strategies); Intention-to-treat (ITT), as treated (AT), 및 per protocol (PP) 분석 접근법이 존재한다. ITT는 배정받은 대로의 분석이라고도 하며, ITT 원칙에서는 치료 계획의 준수 및 이행, 연구의 완료와 상관없이, 초기 군 배정에 따라 모든 참가자의 분석을 시행한다. 이 접근법은 연구 계획에서 예상할 수 있거나 혹은 없는 다양한 상황에서, 현실적인 환경과 유사한 임상 환경을 반영하는 것을 목적으로 한다. PP접근법은 연구 포함 기준(inclusion criteria)에 적합하며, 연구 계획에 따라서 중재를 받았으며, 주요 결과 변수(primary outcome variable)가 측정된 참가자만을 대상으로 분석을 시행한다. 일반적으로, ITT 원칙은 우월성(superiority) 또는 비동등성(inequality) 시험에 선호되는 반면, PP 접근법은 동등성(equivalence) 또는 비열등성(non-inferiority) 시험에 선호된다. 그러나 두 가지 접근 방법을 이용한 분석이 모두 시행되어야 하며, 두 가지 방법에 따라 분석했을 때 그 결과에 유의미한 차이가 있는지 비교하여야 한다. 결국, ITT 및 PP 두 접근법 모두 시행하는 것이 치료 효과에 대하여 더 완벽한 이해를 제공할 수 있으며, 연구 결과의 신뢰성을 보장하는 데 도움이 된다.

Keywords: Data analysis; Intention to treat analysis; Intervention study; Randomized controlled trial; Statistics; Treatment outcome.

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Predicting optimal endotracheal tube size and depth in pediatric patients using demographic data and machine learning techniques

인구통계학적 데이터와 기계 학습 기법을 이용한 소아 환자의 기관내 튜브 최적 크기와 깊이 예측

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배경: 적절한 크기와 깊이를 가진 기관내 튜브(ETT)를 사용하면 소아 환자의 삽관 관련 합병증을 최소화하는 데 도움이 될 수 있다. 그러나 최적의 ETT 크기를 선택하기 위한 기존의 연령 기반 공식은 부정확하다고 보고되었다. 본 연구에서는 인구통계학적 데이터를 사용하여 소아 환자의 ETT의 최적 크기와 깊이를 예측하는 기계 학습 모델을 개발하여 임상 응용을 가능하게 했다.

방법: 기관내 삽관으로 전신마취를 한 12세 미만의 환자 37,057명의 데이터를 후향적으로 분석했다. 그래디언트 부스팅 회귀 트리(GBRT) 모델이 개발되어 전통적인 연령 기반 공식과 비교되었다.

결과: GBRT 모델은 기낭이 없는 ETT와 있는 ETT의 크기(내경 [ID])를 예측하는 데 있어 0.502 (95% CI [0.486, 0.568])와 0.669 (95% CI [0.640, 0.694])의 가장 높은 매크로 평균 F1 점수를 보여 0.163 (95% CI [0.140, 0.196], P < 0.001)과 0.392 (95% CI [0.378, 0.406], P < 0.001)를 산출한 연령 기반 공식을 능가했다. ETT의 깊이(ETT 끝에서 입술 구석까지의 거리)를 예측할 때, GBRT 모델은 기낭이 없는 ETT와 있는 ETT에서 각각 1.18 cm (95% CI [1.16, 1.20], P < 0.001)와 1.34 cm (95% CI [1.31, 1.38], P < 0.001)의 오차를 보여 연령 기반 공식의 0.71 cm (95% CI [0.69, 0.72])와 0.72 cm (95% CI [0.70, 0.74])에 비해 낮은 평균 절대 오차(MAE)를 보였다.

결론: 인구통계학적 데이터만을 이용한 GBRT 모델은 ETT 크기와 깊이를 정확하게 예측하였다. 추후 이러한 결과가 검증된다면, 본 모델은 소아 환자에게 최적의 ETT 크기와 깊이를 예측하는 데 도움이 될 수 있다.

Keywords: Airway management; Demography; General anesthesia; Intratracheal intubation; Machine learning; Pediatrics.

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Association between inflammation-based prognostic markers and mortality of non-cardiac surgery

염증 기반 예후표지자(바이오마커)와 비심장 수술 사망률의 연관성

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배경: 염증 및 영양 기반 바이오마커와 비심장 수술 후 수술 결과의 연관성을 평가하였다.
방법: 2011년 1월부터 2019년 6월까지 C-반응 단백질(CRP), 알부민 및 완전 혈액 수(CBC)를 수술 전 6개월 이내에 측정하여 비심장 수술을 받은 총 102,052명의 환자를 대상으로, CRP 대 알부민 비율(CAR), 호중구 대 림프구 비율(NLR), 혈소판 대 림프구 비율(PLR) 및 수정된 글래스고 예후 점수(mGPS)와 수술 결과의 연관성을 평가하였다. 수신기 작동 특성(ROC) 곡선을 사용하여 최적의 기준값을 추정하였고, 이 값에 따라 환자를 높은 그룹과 낮은 그룹으로 나누어 1년 사망률을 비교하였다.
결과: 전체 환자에서 1년 사망률은 4.2%였다. ROC 분석에 따르면 CAR, NLR, PLR 및 mGPS의 경우 각각 0.796, 0.743, 0.670 및 0.708 곡선 아래의 영역이 나타났다. 추정된 임곗값에 따르면 높은 CAR, NLR, PLR 및 mGPS는 1년 사망률 증가와 연관되었다(1.7% vs. 11.7%, 위험비율 [HR]: 2.38, 95% CI [2.05, 2.76], P < 0.001, CAR의 경우 2.2% vs. 10.3%, HR: 1.81, 95% CI [1.62, 2.03], P < 0.001, NLR의 경우 2.6% vs. 10.5%, HR: 1.86, 95% CI [1.73, 2.01], P < PLR의 경우 0.001, 그리고 2.3% vs. 16.3%, HR: 2.37, 95% CI [2.07, 2.72], P < 0.001).
결론: 수술 전 CAR, NRL, PLR, mGPS는 수술 후 사망률과 연관성을 보였다. 이 결과는 비심장 수술 후 사망률 예측에 도움이 될 수 있다.

Keywords: Biomarkers; General surgery; Inflammation; Mortality; Nutritional status; Patient outcome assessment.

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Does intravenous patient-controlled analgesia or continuous block prevent rebound pain following infraclavicular brachial plexus block after distal radius fracture fixation? A prospective randomized controlled trial

정맥내 환자-조절 진통제 또는 연속 상완신경총 차단은 원위 요골 골절 수술을 위한 쇄골하 상완신경총 차단 후 발생하는 반발통을 예방할 수 있는가? 전향적 무작위 대조 시험

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배경: 본 연구의 목적은 마약성 진통제 기반 정맥내 환자-조절 진통제(intravenous patient-controlled analgesia, IV PCA) 또는 연속 상완신경총 차단(brachial plexus block, BPB)이 상완신경총 차단하에서 시행된 원위 요골 골절 수술 후 발생하는 반발통을 조절하는 역할과 총 마약성 진통제 사용량에 미치는 영향을 규명하는 것이다.

방법: 전위된 원위 요골 골절에 대해 수장측 금속판을 이용하여 수술적 치료를 시행할 예정인 총 66명의 환자를 단일 쇄골하 상완신경총 차단만을 시행 받은 환자군(BPB only group) (n = 22), 단일 쇄골하 상완신경총 차단 후 IV PCA를 가진 환자군(IV PCA group) (n = 22), 단일 쇄골하 상완신경총 차단 후 연속 쇄골하 상완신경총 차단을 시행 받은 환자군(continuous block group) (n = 22)으로 무작위 배정하였다. 통증에 대한 시각적 아날로그 스케일(VAS)과 이용된 진통제의 양을 수술 후 4, 6, 9, 12, 24, 48시간, 그리고 2주째 기록하였다.

결과: 수술 후 9시간에서 통증 VAS 점수는 BPB only group (median: 2; Q1, Q3 [1, 3])에서 IV PCA group (0 [0, 1.8], P = 0.006) 및 continuous block group (0 [0, 0.5], P = 0.009)보다 유의하게 높았다. 수술 후 12시간에서 통증 VAS 점수는 BPB only group (0.5 [0, 3], P = 0.004)보다 continuous block group (3 [3, 4])에서 유의하게 높았다. 총 마약성 진통제 소비량은 IV PCA group (350.3 [282.1, 461.3])에서 BPB only group (37.5 [22.5, 75], P < 0.001) 및 continuous block group (30 [15, 75], P < 0.001)에서 유의미하게 높았다. 그러나 총 마약성 진통제 소비량은 BPB only group과 continuous block group (P = 0.595)에서 유의하게 다르지 않았다.

결론: 연속 쇄골하 상완신경총 차단이 단일 쇄골하 상완신경총 차단에 비해 총 마약성 진통제의 소비량을 감소시키지는 못했지만, 이 방법은 원위 요골 골절에 대한 수술 후 9시간 및 12시간에서 단일 쇄골하 상완신경총 차단 후 발생하는 반발통을 조절하는 데 효과적이다.

Keywords: Brachial plexus blockade; Breakthrough pain; Catheters; Distal radius fracture; Patient-controlled analgesia; Regional anesthesia.

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Quality of recovery in hospital and disability-free survival at three months after major abdominal surgery

복부 수술 후 단기 병원내 회복 정도와 수술 후 3개월 회복 정도와의 연관성

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배경: Quality of Recovery-15 (QoR-15) 및 12-item World Health Organization Disability Assessment Schedule 2.0 scales은 수술 후 환자 보고를 기반으로 하는 결과 척도이다. 연구자들은 수술 후 단기 병원 내 회복과 퇴원 후 장애가 없는 생존(disability-free survival, DFS) 사이의 연관성을 평가하는 것을 목표로 했다.

방법: 전향적 관찰 연구를 수행했으며, 65세 이상의 선택적 주 복부 수술을 받는 암 환자 260명을 등록했다. 수술 후(POD) 2일에서 QoR-15 점수 < 90으로 정의된 수술 후 회복 불량과 3개월 후 DFS 사이의 연관성을 평가했다. POD 2의 회복 불량과 DFS 가능성의 확률비(odds ratio)는 주요 요인(나이, 수술 전 허약, 수술 전 DFS, 수술 기간, 수술 중 혈액 손실량) 등을 조정한 후 다중 로짓 회귀 분석을 사용하여 계산되었다.

결과: 총 230명의 환자가 3개월간의 추적 관찰을 완료하였다. POD 2에서는 환자의 27.3% (63/230)가 회복 불량이었다. POD 2에서 회복이 양호한 환자는 수술 후 3개월 DFS의 빈도가 79.6%로 POD 2회복이 불량한 환자의 DFS 빈도(65.1%)보다 많았다(P = 0.026). POD 2에서의 회복 불량과 3개월 후 DFS 가능성의 조정 확률비는 0.481 (95% CI [0.233, 0.994])이었다.

결론: POD 2에서 회복이 부진한 환자는 복부 수술 3개월 후 DFS일 확률이 낮았다. 이러한 결과는 주요 복부 수술 후 조기에 효과적인 중재를 할 수 있도록 도움을 준다.

Keywords: Aged; General surgery; Neoplasms; Operative surgical procedures; Patient outcome assessment; Postoperative complications.

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Comparison of the pericapsular nerve group block with the intra-articular and quadratus lumborum blocks in primary total hip arthroplasty: a randomized controlled trial

고관절 전치환술에서 피막주위신경군(PENG) 차단, 관절강내 차단, 그리고 허리사각근 차단의 비교: 무작위 대조 시험

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배경: 고관절 전치환술(total hip arthroplasty, THA)에서 피막주위신경군(pericapsular nerve group, PENG) 차단, 허리사각근 차단(quadratus lumborum block, QLB), 그리고 관절강내(intra-articular, IA) 국소마취제 주입은 효과적인 진통 효과를 제공한다고 알려져 있다. 이 무작위 연구는 PENG 차단, 허리사각근 차단, 관절강내 국소마취제 주입의 진통 효과, 운동 보호, 회복의 질을 비교하는 것을 목표로 하였다.

방법: 척추 마취하에 한쪽 고관절 전치환술을 받은 89명의 환자가 PENG (n = 30), QLB (n = 30), IA (n = 29) 그룹에 무작위로 할당되었다. 주요 결과는 수술 후 첫 48시간 동안 통증의 수치평가척도(numerical rating scale, NRS) 점수였다. 이차적 결과는 수술 후 마약성 진통제 소비, 대퇴사두근과 내전근의 근력, 회복의 질(quality of Recovery-40, QoR-40)이었다.

결과: 수술 후 3시간 및 6시간에 이루어진 동적(움직임이 있는) NRS 점수는 PENG 및 QLB 그룹에서 IA 그룹보다 유의하게 낮았다(P = 0.002 및 P < 0.001). 첫 번째 마약성 진통제 요구 시간은 PENG 및 QLB 그룹에서 IA 그룹보다 길었다(P = 0.009 및 P = 0.016). 수술 후 3시간에 대퇴사두근의 근력 보존에 있어 PENG 그룹이 QLB 그룹보다 더 나은 효과를 보였고(P = 0.007), 이동 가능 시간에 있어서도 더 나았다(P = 0.003). QoR-40 점수에 있어서는 유의한 차이가 관찰되지 않았다.

결론: PENG 및 QLB 그룹은 유사한 진통 효과를 보였으며, 수술 후 6시간에 IA 그룹보다 더 효과적인 진통을 제공했다. 모든 그룹에서 수술 후 회복의 질은 유사했다.

Keywords: Anesthesia; Arthroplasty; Lower extremity; Nerve block; Pain management; Postoperative pain.

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Effects of dexmedetomidine on pulmonary function in patients receiving one-lung ventilation: a meta-analysis of randomized controlled trial

일측폐 환기를 받는 환자에서 덱스메데토미딘이 폐 기능에 미치는 영향: 무작위 대조 시험의 메타분석

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배경: 기계적 환기, 특히 일측폐 환기(one lung ventilation)는 폐 기능 장애를 유발할 수 있다. 이 메타분석은 일측폐 환기를 받는 환자의 폐 기능에 대한 덱스메데토미딘(dexmedetomidine)의 효과를 평가하였다.

방법: Embase, PubMed, MEDLINE, Cochrane Library, ClinicalTrials.gov 및 중국 임상 시험 등록 데이터베이스를 체계적으로 검색했다. 주요 결과는 산소화 지수(oxygenation index)였다. 수술 후 합병증의 발생을 포함한 다른 결과를 평가했다.

결과: 845명의 환자를 대상으로 한 14개의 무작위 대조군 시험이 본 메타분석에 포함되었다. 덱스메데토미딘은 일측폐 환기 시작 30분(mean difference [MD]: 40.49, 95% CI [10.21, 70.78]), 60분(MD: 60.86, 95% CI [35.81, 85.92]), 90분(MD: 55, 95% CI [34.89, 75.11]) 후, 그리고 수술 종료 후(MD: 28.98, 95% CI [17.94, 40.0])의 산소화 지수를 향상시켰고, 일측폐 환기 시작 90분 후의 폐 순응도를 향상시켰다(MD: 3.62, 95% CI [1.7, 5.53]). 또한, 덱스메데토미딘은 수술 후 폐 합병증(odds ratio: 0.44, 95% CI [0.24, 0.82])과 입원 기간 (MD: −0.99, 95% CI [−1.25, −0.73]), tumor necrosis factor-α, interleukin (IL)-6, IL-8, malondialdehyde 수준을 감소시켰으며 superioxide dismutase 수준은 증가시켰다. 그러나 민감도 및 시험 순차 분석에서는 산소화 지수 및 IL-6 수준에 대한 결과만 확인되었다.

결론: 덱스메데토미딘은 일측폐 환기를 시행받는 환자의 산소화를 개선하고 추가로 수술 후 폐 합병증의 발생을 감소시키고 입원 기간을 단축시킬 수 있다. 이는 폐 순응도, 항염증 효과 및 산화 스트레스 반응 조절의 개선과 관련이 있을 수 있다. 그러나 이러한 결론을 확인하기 위해서는 더 강력한 증거가 필요하다.

Keywords: Artificial respiration; Dexmedetomidine; Meta-analysis; One-lung ventilation; Postoperative complications; Respiratory mechanics.

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Comparison of different nonsteroidal anti-inflammatory drugs for cesarean section: a systematic review and network meta-analysis

제왕절개술 시 통증조절을 위한 여러 종류의 비스테로이드성 소염진통제의 효과 비교: 체계적 문헌고찰 및 네트워크 메타분석

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배경: 제왕절개술은 중등도 이상의 통증과 관련이 있으며 비스테로이드성 소염제(nonsteroidal anti-inflammatory drugs, NSAIDs)가 일반적으로 사용된다. 그러나 최적의 NSAID는 밝혀지지 않았다. 이 네트워크 메타분석 및 체계적 검토에서는 대조군과 개별 NSAIDs가 진통, 부작용, 회복의 질 지표에 미치는 영향을 비교하였다.

방법: CDSR, CINAHL, CRCT, Embase, LILACS, PubMed, Web of Science에서 일반 마취 또는 부위 마취하에 정규 또는 응급 제왕절개 수술에서 특정 NSAID를 대조군 또는 다른 NSAID와 비교하는 무작위 대조군 시험을 검색했다. 네트워크 플롯과 리그 테이블을 구축하고 근거의 질을 평가하기 위하여 GRADE 분석을 사용했다.

결과: 우리는 47개의 시험을 포함했다. 1,228명의 환자와 18개의 시험에서 1차 결과인 24시간의 누적 정맥 모르핀 등가 소비를 조사한 결과, 대조군은 diclofenac, indomethacin, ketorolac, tenoxicam (심각한 제한, 부정확성 및 출판 편향으로 인해 근거수준이 매우 낮음)보다 열등한 것으로 나타났다. Indomethacin은 8-12시간의 휴식상태에서 통증 점수가 celecoxib보다 우월했고, 48시간의 움직임에 대한 통증 점수가 celecoxib + parecoxib, diclofenac, ketorolac보다 우수했다. 추가 진통제의 필요성과 요구시간에 대해서는, celecoxib류의 COX-2 억제제가 다른 NSAID보다 열등했다.

결론: 우리의 리뷰는 연구된 NSAID들 사이에 최소한의 차이가 존재함을 시사한다. 비선택적 NSAID들이 선택적 NSAID들보다 더 효과적일 수 있고, indomethacin과 같은 일부 NSAID들이 다른 NSAID들보다 더 이상적일 수 있다.

Keywords: Analgesia; Cesarean section; Non-steroidal anti-inflammatory agents; Obstetrical anesthesia; Postoperative pain; Systematic review.

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Effect of magnesium sulfate on oxygenation and lung mechanics in morbidly obese patients undergoing bariatric surgery: a prospective double-blind randomized clinical trial

병적 비만 환자에서 황산마그네슘이 산소화 및 폐 역학에 미치는 영향: 전향적 무작위 눈가림 임상 연구

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배경: 병적 환적 비만 환자에서 호흡 역학은 종종 크게 변화하며 황산마그네슘($MgSO_4$)은 여러 호흡 장애 관리에 유망한 약제이다. 본 연구는 복강경 비만치료 수술을 받는 병적 비만 환자에서 $MgSO_4$ 주입이 동맥 산소화 및 폐 역학에 미치는 영향을 살펴보는 것을 목표로 하였다.
방법: 전신마취하에 복강경 비만 수술이 예정된 21-60세의 병적 비만 환자 40명을 대조군(정상 식염수 주입) 또는 $MgSO_4$ 그룹(30 mg/kg 희박 체중[LBW]을 부하 용량으로 30분 이상 정맥으로 100 ml 정상 식염수에 10% $MgSO_4$를 투여한 다음 90분 동안 10 mg/kg LBW/h를 투여)에 무작위로 할당했다. 1차 결과는 수술 중 동맥 산소화였다. 2차 결과에는 수술 중 정적 및 동적 준수, 사강(죽은 호흡), 혈역학적 매개 변수가 포함되었다.
결과: 수술 중 90분 동안 δ PaO_2/FiO_2 비율과 Δ 동적 폐 준수는 $MgSO_4$ 그룹에서 통계적으로 유의하게 높았다(각각 mean ± SE: 16.1 ± 1.0, 95% CI [14.1, 18.1] 및 8.4 ± 0.5 ml/cm-H_2O, 95% CI [7.4, 9.4]). Δ 사강(%)은 $MgSO_4$ 그룹(mean ± SE: −8.0 ± 0.3%, 95% CI [−8.6, −7.4])에서 통계적으로 유의하게 낮았다. 정적 준수에서 유의한 차이는 관찰되지 않았다.
결론: $MgSO_4$가 병적 비만 환자에서 동맥 산소화를 유의하게 보존하고 동적 폐 순응도와 사강을 유지했음에도 불구하고 임상적 관련성은 미미하다. 본 연구는 이러한 결과의 임상적 중요성을 적절하게 반영하지 못하였다.

Keywords: Anesthesia; Bariatric surgery; Laparoscopy; Magnesium sulfate; Morbid obesity; Respiratory mechanics.

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Effects of sevoflurane on metalloproteinase and natural killer group 2, member D (NKG2D) ligand expression and natural killer cell-mediated cytotoxicity in breast cancer: an in vitro study

세보플루란이 유방암 세포주에서 금속단백분해효소 및 NKG2D 리간드 발현, 그리고 자연살해세포 매개 세포 독성에 미치는 영향: 시험관 내 연구

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배경: 본 연구는 유방암 세포에서 세보플루란 노출이 기질 금속단백분해효소(matrix metalloproteinase, MMP)의 발현, NKG2D 리간드(natural killer group 2, member D; UL16-binding proteins [ULBP] 1–3 and major histocompatibility complex class I chain-related molecules [MIC] A/B)의 발현 및 제거, 그리고 자연살해세포(natural killer cell, NK cell) 매개 세포 독성에 미치는 영향을 조사하기 위해 수행되었다.

방법: 본 연구는 세 가지 인간 유래 유방암 세포주(MCF-7, MDA-MB-453, HCC-70)를 사용하였다. 0 (대조군), 600 (S6), 1200 μM (S12) 농도의 세보플루란을 각각 유방암 세포주에 4시간 동안 처리하였다. 중합효소연쇄반응과 유세포분석법을 활용하여 NKG2D 리간드의 유전자 발현과 단백질 발현을 정량하였으며; 웨스턴 블롯과 효소 결합 면역 흡착 분석법(ELISA)을 이용하여 MMP-1 및 -2의 단백질 발현과 soluble NKG2D 리간드의 농도를 정량하였다.

결과: 세보플루란은 MCF-7, MDA-MB-453 및 HCC-70 세포주에서 모두 용량 의존적으로 NKG2D 리간드 mRNA 및 단백질 발현을 억제했지만, MMP-1 와 -2의 발현이나 soluble NKG2D 리간드 농도에는 영향을 주지 않았다. 또한, 세보플루란은 MCF-7, MDA-MB-453 및 HCC-70 세포주에서 자연살해세포 매개 세포 독성을 용량 의존적으로 감소시켰다(각각 P = 0.040, P = 0.040 및 P = 0.040).

결론: 본 연구는 세보플루란 노출이 용량 의존적으로 유방암 세포주에서 자연살해세포 매개 세포 독성을 약화시킨다는 것을 보여준다. 이러한 결과는 세보플루란에 의한 MMP 발현의 변화보다는 NKG2D 리간드 전사의 감소에 기인하는 것으로 추정된다.

Keywords: Breast neoplasms; Inhalation anesthetics; Matrix metalloproteinases; Natural killer cells; Sevoflurane; Tumor escape.

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What are the best approaches to postoperative pain management after total hip replacement surgery?

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Editorial

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Total hip arthroplasty (THA), with more than 400,000 cases performed annually worldwide, is a common procedure that improves the quality of life of patients with hip pain [1]. As THA is associated with moderate or high pain intensity [2], adequate postoperative pain management without side effects enables early ambulation, facilitates functional recovery, and reduces patient morbidity [1,3].

Peripheral nerve blocks are widely used for postoperative pain management after THA. Clinicians must thus have a clear understanding of the distribution of nerves in the hip joints. The hip joint is innervated by the articular branches of the femoral nerve, obturator nerve, and nerve to the quadriceps femoris. The superior gluteal, inferior gluteal, accessory obturator, and sciatic nerves also contribute to the innervation of the hip joint [4]. The anterior capsule and superior labrum, which have a higher density of nociceptors and mechanoreceptors, appear to be the sources of pain [4]. However, the mechanism of hip joint pain has not yet been clearly identified, and controlling pain with peripheral nerve blocks after THA may be more difficult due to the distribution of multiple nerves to the hip joint. Therefore, various postoperative pain control methods have been used to block the nerves that innervate the hip joint. Additionally, as motor block affects early ambulation, performing only sensory blocks that do not affect muscle strength is helpful for postoperative recovery. Among the various pain control methods after THA, the pericapsular nerve group (PENG) block and quadratus lumborum block (QLB) are used to avoid motor block [5–7].

In this issue of the *Korean Journal of Anesthesiology*, a study comparing the PENG block (PENG group), intra-articular injection (IA group), and QLB (QLB group) for postoperative pain control in patients undergoing primary total hip replacement surgery was reported by Et and Korkusuz [8]. A total of 89 patients were included in the analysis: 30 in the PENG group, 30 in the QLB group, and 29 in the IA group. The dynamic Numerical Rating Scale (NRS) scores at 3 h postoperatively were significantly lower in the PENG and QLB groups than in the IA group ($P = 0.002$ and $P = 0.036$, respectively). At 6 h postoperatively, both the static and dynamic NRS scores in the IA group were significantly higher than those in the PENG ($P = 0.005$ and $P < 0.001$, respectively) and QLB ($P = 0.017$ and $P = 0.002$, respectively) groups. The median (Q1, Q3) time to first opioid requirement was longer in the PENG (11 [8, 14] h) and QLB (11 [6, 14] h) groups than in the IA group (7 [5, 8] h) ($P = 0.009$ and $P = 0.016$, respectively). The frequency of quadriceps muscle paralysis 3 h postoperatively was 23.3%, 63.3%, and 34.5% in the PENG, QLB, and IA groups, respectively ($P = 0.019$). The frequency of quadriceps muscle paralysis 3 h postoperatively was 23.3%, 63.3%, and 34.5% in the PENG, QLB, and IA groups, respectively ($P = 0.019$). Postoperative mean time to mobilization was 13.2 ± 4.4 h in the PENG group, 17.3 ± 4.9 h in the QLB group, and 15.3 ± 6.1 h in the IA group ($P =$

0.011). No significant differences between the groups with respect to the Quality of Recovery-40 score, patient satisfaction, or complications were noted.

These findings suggest that the PENG and QLB techniques may provide superior postoperative pain control at 6 h postoperatively, delay opioid requirements compared to IA injection, and only PENG technique facilitates early mobilization. However, the choice between PENG and QLB should be made considering factors such as muscle strength and opioid consumption, and further research is needed to determine the safety and efficacy of peripheral nerve blocks in the context of enhanced recovery after surgery in THA.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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Pediatric perioperative fluid management

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The purpose of perioperative fluid management in children is to maintain adequate volume status, electrolyte level, and endocrine system homeostasis during the perioperative period. Although hypotonic solutions containing glucose have traditionally been used as pediatric maintenance fluids, recent studies have shown that isotonic balanced crystalloid solutions lower the risk of hyponatremia and metabolic acidosis perioperatively. Isotonic balanced solutions have been found to exhibit safer and more physiologically appropriate characteristics for perioperative fluid maintenance and replacement. Additionally, adding 1%–2.5% glucose to the maintenance fluid can help prevent children from developing hypoglycemia as well as lipid mobilization, ketosis, and hyperglycemia. The fasting time should be as short as possible without compromising safety; recent guidelines have recommended that the duration of clear fluid fasting be reduced to 1 h. The ongoing loss of fluid and blood as well as the free water retention induced by antidiuretic hormone secretion are unique characteristics of postoperative fluid management that must be considered. Reducing the infusion rate of the isotonic balanced solution may be necessary to avoid dilutional hyponatremia during the postoperative period. In summary, perioperative fluid management in pediatric patients requires careful attention because of the limited reserve capacity in this population. Isotonic balanced solutions appear to be the safest and most beneficial choice for most pediatric patients, considering their physiology and safety concerns.

Keywords: Anesthesia; Child; Fluid therapy; Infant; Intravenous infusion; Isotonic solutions; Perioperative medicine.

Introduction

The first intravenous (IV) fluid used in humans was administered to resuscitate a patient dying from malignant cholera [1]. At the earliest stages of IV fluid development, the goal of fluid management was simply to replace intravascular volume loss to recover from hypovolemia. However, hypervolemia was soon found to be as dangerous as hypovolemia. Disturbances in body volume or electrolyte balance can result in impaired organ function and unfavorable outcomes, such as mortality [2,3]. The goal of perioperative fluid management is to maintain homeostasis and central euvolemia and prevent excess salt and water accumulation [4]. To attain a normal physiological state, maintaining or re-establishing extracellular fluid (ECF) volume, blood volume, tissue perfusion, metabolic function, electrolyte balance, and an appropriate acid-base status is necessary [5]. To achieve these goals, Holiday and Segar's formula, commonly called the "4-2-1" rule, has been used to calculate the infusion rate of maintenance fluids. However, the "4-2-1" rule was based on a study that only included healthy persons in non-perioperative settings (Table 1) [6]. Additionally, current pediatric anesthesia clinical practice is consider-

Table 1. The "4-2-1" and "2-1-0.5" Rules

Weight (kg)	Hourly fluid requirement using the "4-2-1" rule (ml/h)	Hourly fluid requirement using the "2-1-0.5" rule (ml/h)
< 10	4 × BW	2 × BW
10–20	40 + 2 × (BW-10)	20 + 1 × (BW-10)
> 20	60 + 1 × (BW-20)	30 + 0.5 × (BW-20)

BW: body weight.

ably different from that in Holiday and Segar's era. Today, we have a better understanding of pediatric physiology, including organ maturation, perioperative fluid and electrolyte requirements, and the effects of preoperative fasting. This review covers the basic terminology, fluid management principles, and fluid physiology relevant to children and the history of IV fluids, appropriate type and volume of intraoperative IV fluids, preoperative fasting management, and the impact of hormonal changes on postoperative fluid management.

We begin with the basic terminology used to describe electrolyte solutions' effect on water movement into and out of the cell.

Osmolarity, osmolality, and tonicity

The osmotic concentration, commonly called "osmolarity," is a measurement of the osmotic activity of electrolyte solutions. Osmolarity is the number of osmoles of solute per volume of solution (Osm/L). Homeostasis is the ability of an organism to maintain a stable internal environment. In humans, this involves the dynamic balance of electrolytes and water in the intracellular fluid (ICF) and ECF, which includes plasma. Disruption of this balance can lead to dehydration, edema, acidosis, alkalosis, and changes in the plasma electrolyte concentrations (e.g., hypo- or hypernatremia).

The osmolarity of a specific solution can be measured using an osmometer or calculated from the composition of the solutes. However, a simple summation of the osmolarity of all solutes in a solution (theoretical osmolarity) is not equal to the measured value (real osmolarity). The osmolarity can be calculated using the following equation [7]:

$$\text{Real osmolarity} = \text{Theoretical osmolarity} \times \text{Osmotic coefficient}$$

For example, a 0.9% Sodium(Na) chloride(Cl) solution has a theoretical osmolarity of 308 mOsm/L (154 mOsm/L Na + 154 mOsm/L Cl), and the osmotic coefficient of the 0.9% NaCl solution is 0.93. If we substitute these numbers in the above equation, we find that the real osmolarity of 0.9% NaCl is 286 mOsm/L (308 mOsm/L × 0.93) [7].

The term "osmolality" is used to express osmotic concentration. To calculate the osmolality, the mass of the solvent is used instead of the volume to define the osmotic concentration. This can be described as the number of osmoles of solute per unit mass of solution, which is Osm/kg H_2O in most solutions for IV use.

The term "tonicity" is used to describe the behavior of a particular solution when a specific cell is fully submerged. The solution is considered hypotonic if the cell swells, with a net movement of water from the solution into the cell, and hypertonic if the cell shrinks, with a net movement of water out of the cell. Isotonic solutions do not alter the cell volume.

Osmolarity and tonicity are different concepts. While both are used to compare the concentration of solutes between two solutions separated by a semipermeable membrane (e.g., the membrane of a human cell), the two terms differ in the definition of effective solutes. Cells can absorb some electrolytes through the cell membrane via specialized transport proteins, which helps to prevent the electrolytes from functioning as osmotically effective solutes *in vivo* [8]. While both permeable and nonpermeable solutes are considered effective for osmolarity, only nonpermeable solutes are considered effective for tonicity. Consequently, an isotonic solution for one species may not be isotonic for another. For example, in the 19th century, scientific societies held the false belief that a 0.6% NaCl solution was isotonic to humans based on experimental data from frogs [9].

The actual osmolarity of human plasma is 288 mOsmol/kg H_2O, which is not significantly different from the theoretical osmolarity of 291 mOsmol/L. Therefore, a solution is considered isotonic to human cells if the sum of the concentrations of the nonpermeable solutes is not significantly different from 290 mOsmol/L.

For example, using an osmometer, the osmolarity of a 0.9% NaCl solution is 286 mOsmol/L. Because both Na and Cl are nonpermeable solutes to human cell membranes, 0.9% NaCl is considered isosmotic and isotonic to human plasma. It is important to note that an isosmotic solution is not always isotonic but can also be hypotonic. For example, although the actual osmolarity of a 5% dextrose water solution (5DW) is 278 mOsmol/L, it is considered hypotonic since, unlike Na or Cl, glucose can completely permeate human cell membranes. When glucose enters the cell, it drags water along with it via osmosis, causing the cell to expand

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in volume. Additionally, glucose metabolizes into energy, carbon dioxide, and water once inside the cell, so 5DW is not different from pure water in terms of tonicity [8].

To summarize, a hypoosmotic solution is always hypotonic, whereas an isosmotic solution can be either hypotonic or isotonic. Hyperosmotic solutions can be hypotonic, isotonic, or hypertonic. For example, a 10% dextrose water (10DW) solution is considered both hyperosmotic and hypotonic in humans.

Now we will discuss how fluid and electrolytes are balanced in children.

Fluid and electrolyte physiology in children

The two-compartment model, which consists of the ECF and ICF, is commonly used to describe body fluids. The ECF to ICF ratio changes continuously as a child grows. The proportion of the ECF to the ICF volume is higher in the fetus (45% vs. 35% of body weight). By 1 month of age, however, the ECF and ICF volumes are equivalent, and the ratio of the ECF to the ICF as seen in adults (1 : 2) is reached by the age of 1–3 years. Given that infants have a relatively high ECF compared to ICF volume, they are more susceptible to dehydration and fluid imbalance.

The proportion of total body fluids to body weight decreases with age. In the fetus, the proportion is as high as 80%, falling to 70% at full term, 60% by the age of 1 year, and 50%–60% after puberty [10]. This decrease in water is primarily due to a decrease in the ECF volume as the ICF volume increases with cell growth. Fortunately, the composition of the ECF, including plasma, is consistent across all ages, which allows for the same electrolyte-containing fluids to be used in adults and children if their kidneys have matured and can appropriately handle the electrolyte concentrations and water volume. The ECF consists of three compartments: the plasma, interstitial fluid, and transcellular fluid. Only 25% of the ECF is plasma; the rest is interstitial fluid. Transcellular fluid consists of the lymph, cerebrospinal fluid, aqueous and vitreous humor, synovial fluid, and serous fluid. The volume of transcelluar fluid is clinically negligible in healthy children (Fig. 1) [11].

Na and Cl are the major electrolytes in the ECF, including in the plasma. The concentrations of potassium (K), phosphate, magnesium, and proteins are higher in the ICF than in the ECF. The composition of the interstitial fluid is similar to that of the plasma, except for lower levels of proteins in the interstitial fluid [12]. This uneven distribution of fluids and electrolytes between the ECF and ICF is mediated by the sodium-potassium adenosine triphosphatase pump (Na-K ATP pump) in the cell membrane (cations) and the Gibbs–Donnan effect (anions). The Na-K ATP pump enables Na and K to be the major cations in the ECF and

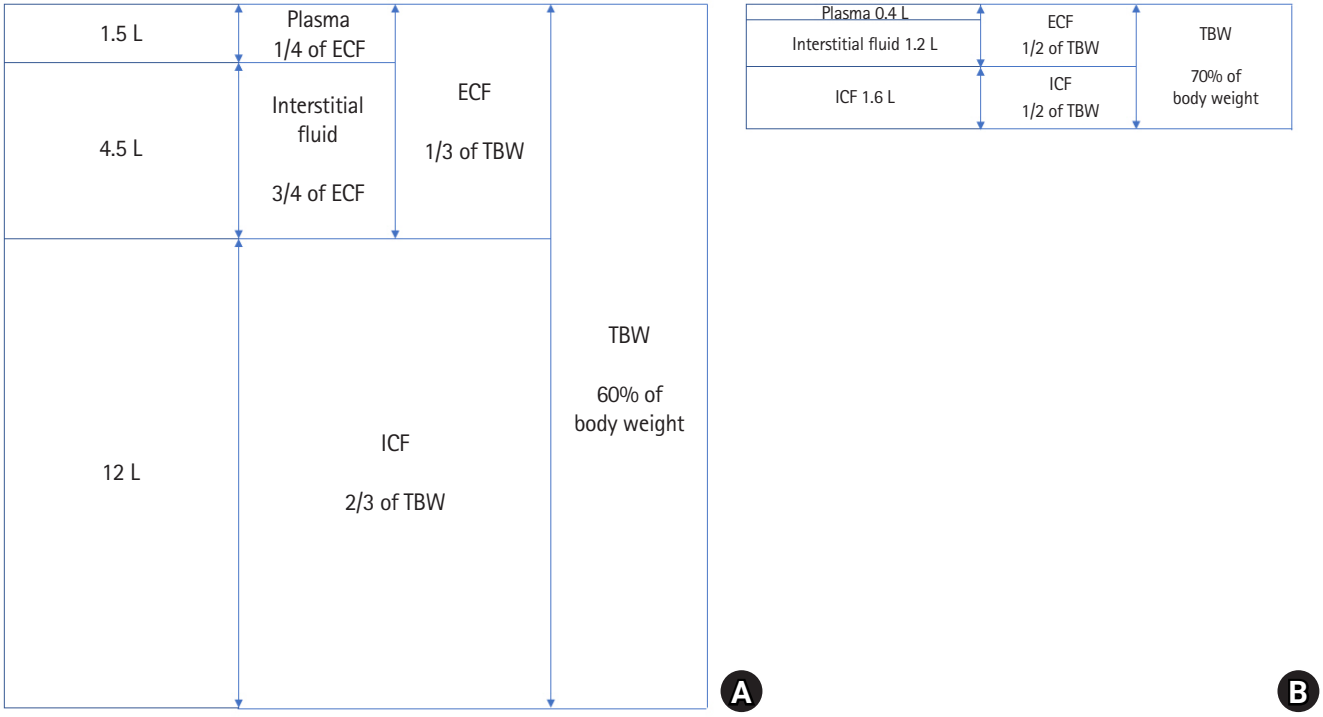

Fig. 1. Distribution of body water in a (A) 30-kg child aged 9 years and (B) 4.5-kg child aged 1 month. The height of a graph is proportional to the volume. ECF: extracellular fluid, ICF: intracellular fluid, TBW: total body water.

ICF, respectively. The Gibbs–Donnan effect is a phenomenon of uneven distribution of diffusible ions between a semipermeable membrane owing to the presence of non-diffusible ions. In body fluids, negatively charged proteins in the ICF cannot cross cellular membranes, making Cl a major anion in the ECF [13].

Electrolyte levels depend on the dynamic equilibrium between intake and output. In healthy children, electrolyte loss occurs primarily through the urine, followed by the skin. A total of 2–3 mEq/kg Na, 1–2 mEq/kg K, and 5 mEq/kg Cl leave the body in urine every day. The loss of Na and K through the skin is much lower (0.5 mEq/kg per day). To compensate for this loss, the daily electrolyte requirements should be as follows: 3 mEq/kg Na, 2 mEq/kg K, and 5 mEq/kg Cl [6,14].

History of IV fluids

In 1628, William Harvey first explained the closed circulation of blood in the human body in his famous book, "*Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*," translated as "An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings." However, the first successful report of plasma replacement appeared approximately 200 years later, after the second cholera pandemic in England [1]. Dr. Thomas Latta was the first to successfully treat cholera with an IV fluid injection in 1832. He wrote "I at length resolved to throw the fluid immediately into the circulation. In this, having no precedent to direct me, I proceeded with much caution." Of the initial four patients who received IV fluids, one patient survived. He attributed the low success rate to the low volumes infused, administration at a late stage of the disease process, and underlying diseases [1]. Latta's initial IV fluid was a mixture of "two drachms of muriate, and two scruples of carbonate of soda, to sixty ounces of water," making it a hypotonic and hyponatremic solution of NaCl and sodium carbonate mixed in water. The concentration was as follows: Na 106 mmol/L, Cl 78 mmol/L, and carbonate 14 mmol/L [15]. This hypotonic solution would induce hemolysis and may thus be related to the high rate of resuscitation failure. Subsequently, Latta modified the solution to be closer to the concentrations in plasma, at 134 mmol/L Na, 118 mmol/L Cl, and 16 mmol/L bicarbonate [16]. However, IV fluid resuscitation did not gain popularity after the sudden death of Latta from pulmonary tuberculosis and the end of the cholera pandemic.

Nearly 50 years passed before a similar physiologic IV solution, designed by Sydney Ringer, appeared in the literature in 1882. Ringer's solution maintained the rhythmicity of frog cardiac muscle in ex vivo studies better than saline, although he believed that 0.6% NaCl was isotonic to human serum, based on frog experiments [17]. In 1888, "normal saline" first appeared in a printed article; however, the composition was far from equivalent to that of the ECF: 150 mmol Na, 128 mmol Cl, 2.5 mmol phosphate, and 27 mmol bicarbonate in 1,000 ml of water [18]. In 1921, Hartog Hamburger published a report that human blood and NaCl 0.9% solution were isotonic, based on a freezing point comparison. The in vitro study conducted by Hamburger provided the first scientific support for the use of a 0.9% NaCl solution [19]. In 1924, Rudolph Matas advocated "the value and advantages of the IV route for the direct and continuous instillation of fluids intended to replace the volume of lost blood," prompting a new era of continuous IV drips [20]. In 1932, the American pediatrician Alexis Hartmann replaced the unstable bicarbonate in Ringer's solution with stable lactate while treating children with metabolic acidosis due to severe diarrhea, emphasizing the advantage of a balanced salt solution [21]. Calcium-free acetate-buffered isotonic solutions (e.g., PlasmaLyte) have recently been introduced into clinical practice. Although a better physiological profile has been associated with a balanced salt solution, even in the 1930s, the 0.9% NaCl solution is still widely used perioperatively [22].

Ideal pediatric intraoperative fluid

Pediatric intraoperative fluid management involves four major considerations. The first is tonicity, which is primarily determined by Na concentration. The second is the use of a balanced solution, with buffered solutions containing less Cl than unbalanced or unbuffered solutions. The third is glucose levels, which are associated with hypoglycemia, lipolysis, ketosis, or even shock if depleted and hyperglycemia if excessive. The fourth is the use of a colloid solution containing protein or starch to maintain intravascular oncotic pressure. Many medical societies have developed guidelines and recommendations to address these issues.

Hyponatremic vs isonatremic solutions

In this section, we will use the terms hyponatremic and isonatremic instead of hypotonic and isotonic to increase understanding of the historical context of hypotonic maintenance fluid solutions in pediatrics.

Holiday and Segar calculated the basal fluid and electrolyte requirements for children. The Na requirement calculated was 3 mEq/100 cal/day [6]. If a child's body weight is 5 kg, the amount of fluid calculated using the "4-2-1" rule is 4 (cc/h/kg) × 5 (kg) × 24 (h/day) = 480 ml/day . Because the "4-2-1" rule is based on the observation that processing one calory requires one milliliter of water, the daily requirement of Na is 3 (mEq/100 cal/day) ×

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480 (ml/cal) = 14.4 mEq/day. For a child with complete oral fasting and minimal movement, 480 ml of water and 14.4 mEq of Na should be supplied daily; an IV fluid solution containing 30 mEq/L Na (14.4 mEq/0.48 L = 30 mEq/L) can be used. This is the same Na concentration as that of 0.18% NaCl with 4% glucose (154 mEq/L × 0.2 = 31 mEq/L), which is only 21.4% of the Na concentr ation of human plasma (140 mEq/L × 0.214 = 30 mEq/L). This is the rationale for using 0.18% NaCl with 4% glucose as the maintenance solution for neonates and infants; however, this is actually a hyponatremic solution. In the 1960s and early 1970s, severe hyponatremic fluids, such as 0.2% NaCl or even 5% dextrose water (which contains no Na) was used as a maintenance and replacement fluid perioperatively because of the false belief that children's immature kidneys could not excrete Na properly. Although subsequent studies have demonstrated that the concentration function of the kidney matures rapidly, reaching 80–90% of adult levels by six months of age, the universal practice of administering hyponatremic solutions during anesthesia persisted. Because Na is the primary determinant of the osmolarity of a solution, a hyponatremic solution is hypotonic in most cases. When administered over a short period, such severely hypotonic fluids can induce acute cerebral edema and, ultimately, brain herniation due to the net movement of water. Prepubescent children are more vulnerable to hyponatremia-induced brain edema than adults because of their increased brain-size-to-cranial-vault ratio, decreased Na-K ATPase activity, and increased antidiuretic hormone (ADH) levels in response to stress [23,24]. Children who receive hyponatremic fluids may experience increased irritability, headaches, seizures, and even sudden death [24,25]. In 2014, a Cochrane review compared isotonic and hypotonic solutions as maintenance IV fluids in children. This review included ten studies with 1,106 total patients. Most patients were admitted to an intensive care setting. The risk of hyponatremia was decreased by 52% in the isotonic solution group [26]. This finding is consistent with that of a well-designed double-blind randomized controlled trial (RCT) comparing an isotonic IV fluid containing 140 mmol/L Na to a hypotonic solution with 77 mmol/L Na as the IV maintenance fluid in children. The group that received the isotonic fluid had a lower risk of hyponatremia, with no increase in adverse effects [27].

Even in the 1960s, Holliday was also aware of the risk of hyponatremia associated with large volumes of hypotonic solution [28,29]. Although he recommended isotonic solutions for volume expansion or compensation for volume deficits, he still preferred hypotonic solutions for maintenance [30]. However, considering practical concerns, such as the need for additional IV lines and situations requiring rapid volume expansion, isotonic fluids are more appropriate for intraoperative use.

0.9% NaCl solutions vs balanced crystalloid solutions

Although 'normal' is too broad and vague of a term, we call 0.9% NaCl a 'normal' saline solution. Unfortunately, no scientific background supports the use of the word 'normal' for the 0.9% NaCl solution, which consists of 9 g NaCl in 1,000 ml of water. Although this solution is isotonic to human blood, this does not mean that it is normal or physiologic [31].

Moreover, the term 'normal' in normal saline gives a false sense of security, making it dangerous since the human response to a 0.9% NaCl solution may not be benign. Even in healthy volunteers, a large volume infusion of 0.9% NaCl has been associated with abdominal discomfort, pain, nausea, drowsiness, and decreased mental capacity to perform complex tasks [32]. Hyperchloremia, metabolic acidosis, fluid retention, renal vascular constriction, and reduced glomerular filtration rate can also occur in both adults and children following a 0.9% NaCl infusion [34–37]. Additionally, this solution can cause cellular dysfunction by inducing cytosolic acidification, membrane hyperpolarization, inactivation of protein kinases, and disruption of phosphorylation [38]. Although the 0.9% NaCl solution is isotonic to human plasma, it can induce pathological changes in humans. Therefore, caution is advised in calling this solution 'normal.'

A balanced crystalloid solution (BCS) is physiologically more similar to human plasma than the 0.9% NaCl solution. A BCS contains lactate, acetate, or malate as a bicarbonate precursor to prevent hyperchloremic and dilutional metabolic acidosis, which is observed after 0.9% NaCl infusions. Compared to lactate, acetate metabolism is significantly faster and more independent of hepatic function, with a lower increase in oxygen consumption and no interference with the diagnostic use of lactate as a marker of inadequate tissue perfusion [8]. A BCS can be used to normalize electrolyte imbalance, maintain homeostasis, and provide a margin of safety in cases of accidental hyperinfusion [39]. In a well-designed RCT of critically ill adults, the use of a BCS was associated with a lower rate of death and new renal replacement therapy than the use of a 0.9% NaCl solution [40]. In adult patients with sepsis, the beneficial effect of a BCS on mortality was greater than that of saline when fluid choice was controlled earlier [41]. Among non-critically ill adults, the incidence of major adverse kidney events within 30 days was lower with a BCS than with 0.9% NaCl [42]. A recent meta-analysis of 13 studies showed that the BCS was associated with lower hospital or 28–30 day mortality in critically ill adults [43]. However, the mortality and acute kidney injury rates did not differ between the BCS and 0.9%

NaCl solution groups in a Cochrane review of critically ill adult and pediatric patients. However, it should be noticed that, only 258 pediatric patients were included in this Cochrane review [44].

A recent meta-analysis of three RCTs with 162 critically ill pediatric patients showed that metabolic acidosis and bicarbonate levels improved after 4–12 h of hydration with a BCS compared with a 0.9% NaCl solution [45]. The European Society of Pediatric and Neonatal Intensive Care recently conducted a systematic review and published recommendations for IV maintenance fluid therapy. In solid consensus, isotonic BCS was recommended as a maintenance fluid in acute and critically ill children [46]. The European consensus statement in 2011 and guidelines from the Association of the Scientific Medical Societies in Germany in 2016 also recommend an isotonic BCS be used for intraoperative maintenance fluid therapy in children [5,47].

Glucose

During surgery, surgical stress increases plasma counter-insulin hormone levels (e.g., cortisol, glucagon, epinephrine, and growth hormone) and decreases plasma insulin levels, which leads to a hyperglycemia-induced catabolic state [48]. However, if the glucose supplement is insufficient (e.g., long preoperative fasting with no glucose supplement during surgery), lipolysis and ketogenesis occur after depletion of glycogen and gluconeogenetic substrates (e.g., alanine from skeletal muscle) [49]. This leads to a lower or lower-normal glucose concentration, elevated levels of ketone bodies and free fatty acids, reduced base excess, and the occurrence of ketoacidosis [50].

To prevent hypoglycemia and catabolic reactions, fluids containing 5% glucose (5DS) have gained popularity as a maintenance infusion for children [23]. However, as the glucose concentration of 5DS is 5,000 mg/dl, which is approximately 50 times higher than that in plasma, perioperative infusion of 5DS can induce hyperglycemia [50].

In pediatric patients, both hypoglycemia and hyperglycemia are associated with neuronal damage [51]. To minimize the risk of glucose and endocrine homeostasis disruption (hyperglycemia, hypoglycemia, lipid mobilization, and ketosis), recent consensus guidelines recommend 1%–2.5% glucose-containing solutions be used as perioperative maintenance fluids for children [47,52].

However, the amount of glucose administered should be individualized, and the anesthesiologist should monitor plasma glucose levels regularly. By adhering to the recommended preoperative fasting time for a healthy child past the neonatal stage, the administration of a glucose-free solution is unlikely to disrupt glucose and lipid homeostasis during brief ($<$ 1 h), minimally traumatic surgery such as inguinal hernia repair [53]. In fact, the incidence of preoperative hypoglycemia is between 0% and 2.5% and is usually associated with a longer duration of fasting. Accordingly, routine administration of glucose is not necessary in healthy children. In contrast, for a child at a high risk of hypoglycemia, a 2.5% glucose- containing solution may not be sufficient to prevent perioperative hypoglycemia and ketosis [54]. Children in a catabolic state and/or with a low glycogen reserve (e.g., long fasting time, burns, prematurity, debilitation, malnourishment, and liver disease) are at a higher risk of perioperative hypoglycemia. One RCT found that a 2%–4% DS administered at a rate of 10 ml/kg/h was more effective at preventing intraoperative catabolism, insulin resistance, rebound hyperglycemia, and acidosis than a 1% DS in low-birth- weight neonates [55].

Colloids

The use of colloids in clinical practice is relatively new in medical history. The first case series of IV human albumin (HA) use was published in 1941 for severely burned and injured sailors during World War II [56]. Albumin is an essential component of human plasma proteins. The human liver synthesizes 10–12 g of albumin, which is degraded spontaneously daily. The half-life of albumin in human plasma is up to 3 weeks [57]. Albumin comprises more than 50% of plasma proteins and is responsible for 80% of the intravascular oncotic pressure [58]. Besides maintaining oncotic plasma pressure, albumin increases plasma concentrations of thiols, which are essential antioxidants of the ECF [59], modulates the activity of nitric oxide by generating an S-nitroso adduct of serum albumin [60], and acts as a buffer for hydrogen ions [61]. However, few studies have shown that external albumin administration has a clinical impact on these mechanisms.

The use of HA in clinical settings remains controversial. HA administration has not been found to decrease mortality in critically ill adults [62–64]. The actual intravascular volume expansion efficacy of albumin in clinical settings, when compared with that of a crystalloid solution, is often much less than theoretically expected. The theoretical volume expansion efficacy of albumin can be achieved under the conditions of an intact vascular barrier and normal permeability. However, critical illness and inflammatory responses are frequently associated with the degradation of the endothelial glycocalyx layer and increased vascular permeability, which facilitate water and solute leakage into the interstitium. This could partly explain the lack of clinical benefit associated with HA in critically ill patients with edema or sepsis.

HA is the scarcest and most expensive colloid besides plasma. Additionally, HA has a high associated risk of infection. There-

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fore, since the 1970s, synthetic colloids such as the hydroxyethyl starch solution (HES) have gradually replaced HA in clinical practice [65].

The HES is a corn- or potato-based starch containing 0.9% saline or balanced crystalloids. Each HES has a unique molecular weight, degree of substitution, C2/C6 ratio, and concentration. The third-generation HES has a lower molecular weight of 130,000 Da and shows an improved safety profile with a lower risk of renal failure and pruritus and fewer hemostatic alterations, while maintaining the same volume effects [66,67]. The third-generation HES in a balanced electrolyte solution showed fewer acid-base and electrolyte alterations than 0.9% saline [68].

However, the use of a HES in adults, especially under critical conditions, has been controversial. A recent large meta-analysis showed that the HES is associated with an increased risk of blood transfusions and renal replacement therapy in critically ill patients. However, immediate 30- and 90-day mortality rates did not differ significantly [69]. In another meta-analysis, compared with a low-molecular-weight (third-generation) HES in patients with septic shock, a first- or second-generation HES was associated with a significant risk of acute kidney injury and renal replacement therapy, whereas the third-generation HES was associated with an increased risk of renal replacement therapy but not acute kidney injury [70].

In pediatric patients undergoing surgery, a meta-analysis of nine RCTs showed that perioperative volume expansion with a third-generation HES did not alter renal function, blood loss, or blood transfusions [71]. The intraoperative use of a 6% HES 130/0.4 up to 30 ml/kg was not associated with postoperative acute kidney injury in pediatric cardiac patients [72]. However, HES products are under regulatory suspension for all ages in Europe and the USA [73,74].

Pediatric intraoperative fluid management

The most favored intraoperative maintenance fluid is an isotonic BCS with 1%–2.5% glucose. This solution helps to maintain electrolyte and endocrine homeostasis in children during surgery. The "4-2-1" rule, along with the additional fluid requirements based on the invasiveness of the surgical procedure (2 ml/kg/h for minor, 4 mg/kg/h for intermediate, and 6 ml/kg/h for major trauma) is still useful for calculating intraoperative maintenance in children. Anesthesiologists should carefully monitor the ongoing blood and fluid loss and compensate for this loss with an isotonic BCS free of glucose or blood, as necessary. Individualized volume replacement helps optimize the cardiac output based on dynamic variables specific to pediatric patients and their vital signs [75]. Colloids can be added to compensate for volume loss and to maintain the plasma oncotic pressure.

Preoperative fasting

The fasting time associated with volume deficits influences intraoperative fluid management. Prolonged fasting is associated with patient discomfort, nausea and vomiting, thirst, hunger, anxiety, and metabolic changes, including ketoacidosis. However, these adverse effects are less likely to occur when the traditional "6-4-2" fasting guideline is strictly followed [76]. Excessive fasting is common, with some patients fasting for up to 15 h, which is much longer than the recommended fasting time of 2 h [77,78]. Recent studies have suggested that shorter clear-fluid fasting durations may be more beneficial. Two well-designed multidisciplinary approaches that included educating parents and medical personnel and encouraging clear fluid intake even up to 2 h before surgery, failed to reduce the clear fluid fasting time. In contrast, after changing the minimum fasting time to 1 h, prolonged fasting decreased by more than 50% [79,80]. The residual volume of the stomach and gastric pH did not differ between the 1-h and 2-h clear fluid fasting groups [81]. Pooled data and audits of liberal fluid intake guidelines have shown that clear fluid in the stomach of children during the induction of elective anesthesia does not increase the risk of aspiration [82].

In 2022, the European Society of Anesthesiology and Intensive Care published updated guidelines for preoperative fasting in children in which the 6 (solid, infant formula) - 4 (breast milk) - 2 (clear fluid) regimen was changed to the 6 (solid) - 4 (infant formula) - 3 (breast milk) - 1 (clear fluid) regimen (each number representing the minimal hours of fasting) [83]. This reduction in the recommended preoperative clear fluid fasting time is consistent with the 2018 consensus statement from the European Society for Pediatric Anesthesiology (ESPA) [84]. Although this minimum recommended clear-fluid fasting time may be controversial, achieving the shortest possible fasting time without compromising patient safety is essential. The ESPA recommends ≤ 3 ml/kg of clear fluid based on a study examining serial magnetic resonance imaging, which showed that the residual gastric volume returned to baseline 1 h after ingestion of 3 ml/kg sugared clear fluid [85].

Postoperative fluid management

Children should start drinking fluids as early as possible after anesthesia. However, timing should be based on the child's urge to drink. Forced postoperative drinking is associated with in-

creased vomiting [83]. When early oral intake is not possible or insufficient, IV fluid support is essential to maintain normovolemia. Postoperative IV fluid management involves two unique aspects: ongoing body fluid loss and free water retention. Table 2 shows the composition of body fluids. Most body fluids are isotonic; however, they can be hyponatremic or isonatremic. Using a hyponatremic solution as a postoperative maintenance fluid is associated with a high risk of iatrogenic hyponatremia.

Free water retention following surgery is another cause of iatrogenic hyponatremia. Renin and ADH are released to retain salt and water in response to perioperative hypovolemia. Renin promotes Na and water retention via aldosterone, while ADH induces water resorption via the water channels of the collecting tubules and ducts in the kidneys. Intravascular volume depletion is the most potent stimulus of ADH release. Although this reaction is physiological and thus not inappropriate, various osmotic and non-osmotic factors, including pain, inflammation, surgical stress, hypoxia, hypercapnia, sepsis, organ dysfunction, and drugs potentiate the release of excessive amounts of ADH, causing the syndrome of inappropriate antidiuretic hormone secretion (SIADH) to occur [86]. Children in the postoperative period are at risk of dilutional hyponatremia.

To compensate for body fluid loss and free water retention and to minimize the risk of iatrogenic hyponatremia, the postoperative maintenance solution should be isotonic and isonatremic [27]. If a patient has a risk of water retention associated with ADH secretion, restricting fluids to 50%–80% of routine maintenance can be considered.

Even in 1972, Holliday recommended that the maintenance fluid infusion rate be reduced to half of the "4-2-1" rule when the urine output is decreased due to ADH secretion [87]. In 2007, he modified his maintenance fluid therapy recommendations for

Table 2. Composition of Body Fluids

Source	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)	pH	Osmolarity (mOsm/L)
Gastric	50	10–15	150	0	1	300
Pancreas	140	5	0–100	100	9	300
Bile	130	5	100	40	8	300
Ileostomy	130	15–20	120	25–30	8	300
Diarrhea	50	35	40	50		
Sweat	50	5	55	0	Alkaline	
Blood	140	4–5	100	25	7.4	285–295
Urine	0–100	20–100	70–100	0	4.5–8.5	50–1400

Modified from Herrin JT. Fluids and electrolytes. In: Manual of Pediatric Therapeutics. 6th ed. Edited by Graef JW: Philadelphia, Lippincott-Raven. 1997, pp 63–75.

Table 3. Composition of Plasma and Crystalloid Fluids

	Na^+ (mEq/L)	Cl^- (mEq/L)	K^+ (mEq/L)	Ca^{2+} (mEq/L)	Mg^{2+} (mEq/L)	Glucose (g/L)	Lactate (mEq/L)	Acetate (mEq/L)	Gluconate (mEq/L)	Osmolarity (mOsm/L)	pH
Blood											
Plasma	135–145	94–111	4.5–5.0	2.2–2.6	0.8–1.0	0.07–0.1	1–2			275–295	7.4
Isotonic solution											
0.9% Sodium Chloride	154	154								308	5.6
Hartmann's solution	131	111	5.4	1.8			28			280	6
Plasmalyte-A	140	98	5		3			27	23	294	7.4
Hypotonic Solution											
5% Dextrose in Water						50				280	4
0.45% Sodium Chloride	77	77								154	5.6
0.3% Sodium Chloride with 3.3% Dextrose (1 : 2 DS)	51	51				33				288	4.5
0.18% Sodium Chloride with 4% Dextrose (1 : 4 DS)	30	30				40				284	4.5

Plasma and isotonic solution. Modified from Semler MW, Kellum JA. Balanced crystalloid solutions. Am J Respir Crit Care Med 2019; 199: 952–60. Hypotonic solution: from manufacturer's data sheet.

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acutely ill and mild-to-moderately hypovolemic children with ADH secretion. He recommended that 20–40 ml/kg of isotonic solution be administered rapidly within 1–2 h to stop the secretion of ADH and that hypotonic solution be administered per his original recommendation, with the rate reduced by half of the "4-2-1" rule [88]. However, he was a pediatrician and not a pediatric anesthesiologist, and his recommendation was not intended for the postoperative state. As previously mentioned, because of other ADH-stimulating factors, recovery from hypovolemia is not sufficient to stop the secretion of ADH during and after surgery.

Thus, during the postoperative period, the fluid management priority is early oral fluid intake based on ameliorating thirst. If parenteral fluid management is necessary, isotonic solutions should be used as maintenance fluids in children, and the rate should be half of the "4-2-1" rule (i.e., the "2-1-0.5" rule) when hourly urine volume is diminished due to ADH secretion. After urine volume is normalized, the rate may be increased to again follow the "4-2-1" rule (Table 1).

Conclusion

For perioperative fluid management, anesthesiologists should be aware of the perioperative pathophysiology of children and the characteristics of the fluids (Table 3). Excessive preoperative fasting is associated with discomfort, dehydration, and a catabolic state. The preoperative fasting time should be kept to a minimum to ensure patient safety. An isotonic balanced solution shows better physiological characteristics and is safer for perioperative maintenance and replacement than other fluids. For intraoperative maintenance, adding 1%–2.5% glucose can help prevent glucose and endocrine homeostasis disruption in some patients. During the postoperative period, children should be encouraged to drink fluids when thirsty. The rate of postoperative fluid administration should be adjusted to account for the effects of free water retention by renin and ADH as well as ongoing fluid and blood loss during the postoperative period.

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No potential conflict of interest relevant to this article was reported.

Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Intention-to-treat versus as-treated versus per-protocol approaches to analysis

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Randomized controlled trials (RCTs) are considered the most rigorous study design for testing hypotheses and the gold standard for evaluating intervention effectiveness. However, RCTs are often conducted under the assumption of ideal conditions that may differ from real-world scenarios in which various issues, such as loss to follow-up, mistakes in participant enrollment or intervention, and low subject compliance or adherence, may occur. There are various group-defining strategies for analyzing RCT data, including the intention-to-treat (ITT), as-treated, and per-protocol (PP) approaches. The ITT principle involves analyzing all participants according to their initial group assignments, regardless of study completion and compliance or adherence to treatment protocols. This approach aims to replicate real-world clinical settings in which several anticipated or unexpected conditions may occur with regard to the study protocol. For the PP approach, only participants who meet the inclusion criteria, complete the interventions according to the study protocols, and have primary outcome data available are included. This approach aims to confirm treatment effects under optimal conditions. In general, the ITT principle is preferred for superiority and inequality trials, whereas the PP approach is preferred for equivalence and non-inferiority trials. However, both analytical approaches should be conducted and their results compared to determine whether significant differences exist. Overall, using both the ITT and PP approaches can provide a more complete picture of the treatment effects and ensure the reliability of the trial results.

Keywords: Data analysis; Intention to treat analysis; Intervention study; Randomized controlled trial; Statistics; Treatment outcome.

Gap between real and ideal

A randomized controlled trial (RCT) is an experimental research design in which researchers introduce one or more interventions and subsequently observe the outcomes [1]. Scientifically rigorous methodologies such as randomization and blinding are typically applied in RCTs. Randomization ensures that each participant has an equal chance of being assigned to one or more interventions, eliminating the potential bias that may arise if researchers arbitrarily or intentionally assign participants to intervention groups [2]. Blinding of participants, investigators, observers, data analysts, and/or others involved in the study to the assigned groups reduces or eliminates biases that may arise from deviations from the intended intervention and/or biases in the measurement of outcomes [1]. Therefore, RCTs are considered the most scientifically rigorous study design for testing hypotheses and the gold standard for evaluating the effectiveness of interventions. RCTs are considered to provide a high level of evidence regarding the effectiveness of the interventions [3].

RCTs are assumed to be conducted under ideal conditions, which may differ from real-world scenarios. In an ideal setting, all eligible participants are randomly assigned to the intervention groups, meet the eligibility and inclusion criteria, follow the trial protocols perfectly with no loss to follow-up, and have no missing data. In this ideal setting, which subjects need to be included in analysis is obvious. The trial design and implementation should strive to achieve this ideal scenario as much as possible. However, in practice various situations may arise, such as loss to follow-up, mistakes in enrollment or intervention, and low subject compliance (passive behavior) or adherence (more positive, proactive behavior). These situations, which RCT researchers frequently encounter, are collectively referred to as "non-compliance," "non-adherence," or missing data [4].

Bias caused by non-compliance or non-adherence to study protocols

In clinical studies, participants may not always comply with or adhere to study protocols. They may forget to attend interventions or take medications, intentionally or unintentionally undergo other interventions or medications, fail to achieve proper outcomes, or withdraw from the study. Occasionally, researchers may also inadvertently enroll patients who do not meet the eligibility and inclusion criteria for the study. Strategies for dealing with non-compliance, non-adherence, or missing data (i.e., whether to include, exclude, or impute them) can affect the study results. Given that researchers hold conflicting beliefs regarding these strategies, disagreements can often occur. Therefore, researchers must have a good understanding of group-defining strategies to effectively plan how to handle non-compliance, non-adherence, or missing data in advance.

There are various group-defining strategies for analyzing RCT data, including the intention-to-treat (ITT), as-treated (AT), and per-protocol (PP) approaches, which may lead to different results. For example, if a researcher or analyst wants to demonstrate a positive result for an intervention compared to a control in a clinical trial, they may choose an optimistic group-defining strategy. However, this can lead to the overestimation of treatment effects, false positives, and conflicts between researchers. Therefore, it is important to plan in advance the group-defining strategy that will be used and clearly state it in the study protocol. Any possible issues such as inappropriate enrollment, protocol violations, withdrawals, and missing values should also be defined and addressed in advance. Specifically, the definitions and statistical strategies for PP and AT should be addressed in detail. Selecting a group-defining strategy after data collection can introduce researcher and analyst bias.

Owing to the growing recognition of the importance of evidence-based medicine, the number of meta-analyses and network meta-analyses published that quantitatively synthesize the results of RCTs has increased [5,6]. In meta-analyses or network meta-analyses, the choice of group-defining strategies among ITT, AT, and PP can result in significantly different outcomes [7]. Overall, careful planning and transparency are essential for the appropriate handling of non-compliance, non-adherence, or missing data in research studies.

Study example

A virtual study example was designed to demonstrate the different group-defining strategies for analyzing RCT data (i.e., ITT, AT, and PP). This virtual study aims to compare the severity of postoperative sore throat in patients who undergo surgery under general anesthesia in the supine position within 2 h. Twelve patients were randomly assigned to two groups: six in the streamlined liner of the pharyngeal airway (SLIPA) group and six in the intubation group. Patients with diabetes, gastroesophageal reflux, neurological diseases, musculoskeletal diseases, or ankylosing spondylitis were excluded. The primary outcome was the severity of postoperative sore throat measured using the visual analog scale (VAS) at 2, 4, 12, 24, and 48 h postoperatively.

The ideal scenario would be for patients to complete the trials as soon as they are randomized and allocated. However, unexpected events can occur in real-world settings. For example, patients E and F in the SLIPA group received endotracheal intubation because of the difficulty in SLIPA insertion to complete the trials. Although this can occur at any time in the clinical setting, it complicates comparisons between the SLIPA and intubation groups (Fig. 1A).

Various group-defining strategies were used to compare the SLIPA and intubation groups. For group-defining strategy 1, the six patients (A, B, C, D, E, and F) randomized to the SLIPA group are compared to the six patients (G, H, I, J, K, and L) randomized to the intubation group (Fig. 1B). For group-defining strategy 2, the four patients (A, B, C, and D) who underwent an SLIPA are compared with the eight patients (E, F, G, H, I, J, K, and L) who underwent intubation, regardless of group assignment (Fig. 1C). For group-defining strategy 3, the four patients (A, B, C, and D) in the SLIPA group are compared to the six patients (G, H, I, J, K, and L) in the intubation group (Fig. 1D).

For practical purposes, applying group-defining strategy 2, which compares patients who actually underwent an SLIPA insertion and intubation, is appropriate. However, let us assume that

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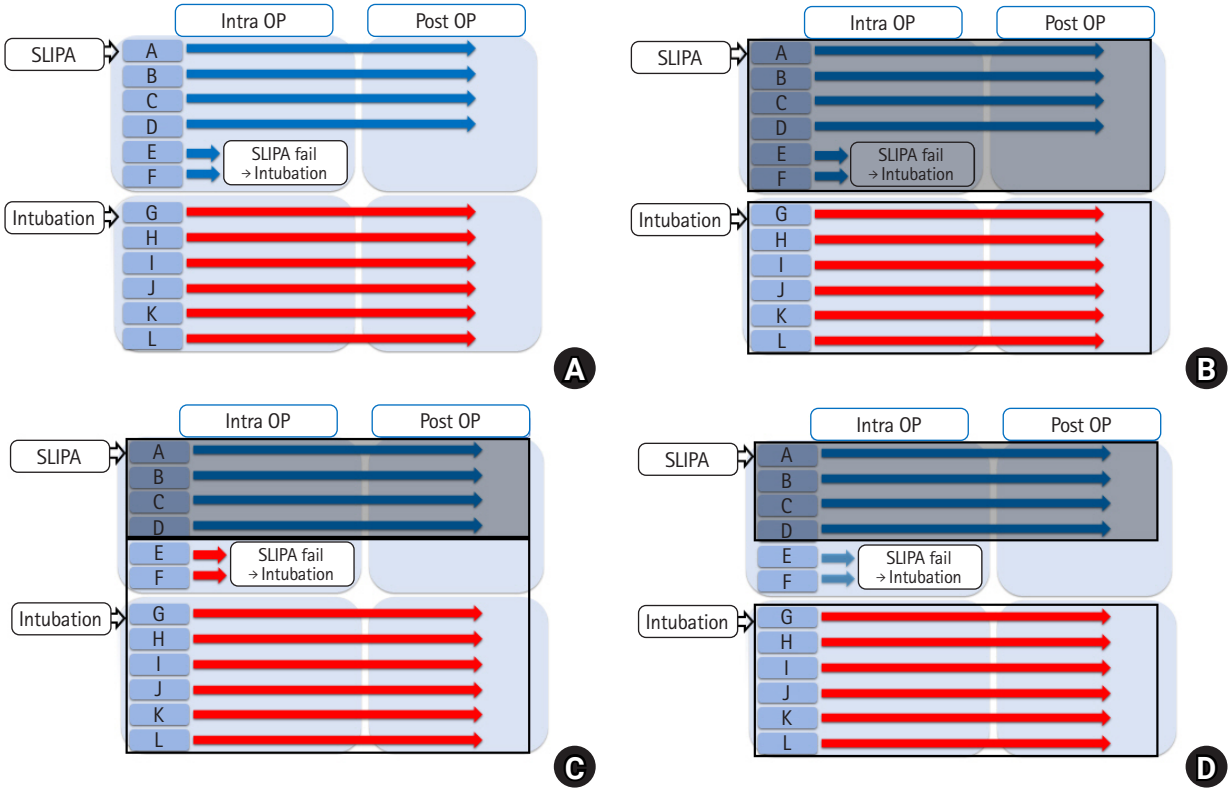

Fig. 1. Virtual study example. (A) Study flow diagram, and (B) intention-to-treat, (C) as-treated, and (D) per-protocol approaches. Twelve patients were randomly assigned to the streamlined liner of pharyngeal airway (SLIPA) (n = 6) and intubation (n = 6) groups. Patients E and F in the SLIPA group received endotracheal intubation instead of SLIPA owing to difficulty with SLIPA insertion for completing the trials. The transparent rectangle refers to the subjects included in the intubation group, while the opaque rectangle represents the SLIPA group. (D) The faint arrow indicating patients E and F shows the subjects who were ultimately excluded from the study.

the two patients with failed SLIPA insertions had abnormal airway anatomies, which contributed to the sore throat postoperatively. As the patients were randomized into the groups, let us assume that the intubation group would have approximately two patients with abnormal anatomies. However, we do not know the identity of these patients. For simplicity, we refer to these patients as patients K and L.

For group-defining strategy 3, the patients (E and F) with abnormal airway anatomy were not included in the SLIPA group, while the intubation group included two patients (K and L) with abnormal anatomies (Fig. 1D). This is not a fair comparison of the two groups as it introduces bias. For group-defining strategy 2, no patients with abnormal airway anatomies were included in the SLIPA group, while four patients (patients E, F, K, and L) with abnormal anatomies were included in the intubation group (Fig. 1C), potentially introducing more bias than group-defining strategy 3.

Group-defining strategy 1 is the only approach that fairly compares the two groups, as it includes two participants with abnormal airway anatomies in each group (Fig. 1B). Thus, the randomized nature of group-defining strategy 1 allows for a more unbiased comparison of postoperative pain between the two groups. Strictly speaking, however, group-defining strategy 1 is a comparison of the severity of postoperative sore throat after the SLIPA, or intubation if SLIPA is not possible, and intubation.

However, performing a clinical study is complex and challenges in clinical research and data analysis are often met, as shown in Fig. 2A. For example, outcome data for patient D in the SLIPA group could not be obtained owing to loss to follow-up, and patients E and F in the SLIPA group received endotracheal intubation instead of SLIPA owing to difficulty with SLIPA insertion. In the intubation group, patient J expired during surgery, the researcher unintentionally inserted an SLIPA into patient K, and patient L was found to have a history of diabetes, and thus should have been excluded according to the exclusion criteria.

Researchers also face several challenges during data analysis. First, they need to decide whether to include or exclude subjects who do not meet the inclusion criteria (e.g., patient L). Second,

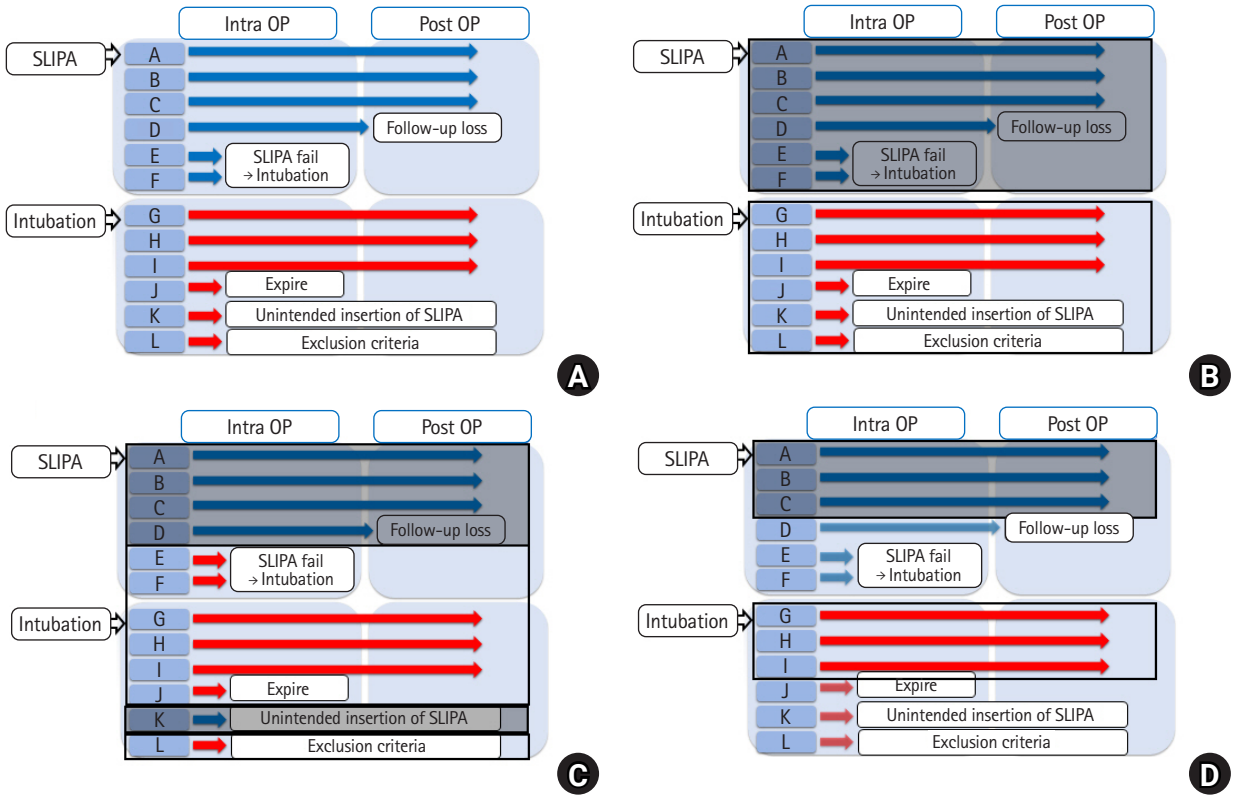

Fig. 2. Complex study example. (A) Study flow diagram and (B) intention-to-treat, (C) as-treated, and (D) per-protocol approaches. Twelve patients were randomly assigned to the streamlined liner of pharyngeal airway (SLIPA) (n = 6) and intubation (n = 6) groups. Patient D was lost to follow up, and patients E and F in the SLIPA group received endotracheal intubation instead of SLIPA owing to difficulty with SLIPA insertion. Patient J expired during the surgery. The researcher unintentionally inserted an SLIPA into patient K, and patient L in the intubation group was found to have a history of diabetes and should have been excluded during enrollment. The transparent rectangle refers to the subjects included in the intubation group, while the opaque rectangle represents the SLIPA group. (D) The faint arrow indicating patients D, E, F, J, K, and L shows the subjects who were ultimately excluded from the study.

for the participants who received a different intervention than the randomized group they were assigned to, researchers must decide which group to include them in (e.g., patients E, F, and K). Third, they need to decide whether to exclude or include patients with missing data (e.g., patients D and J). Additionally, if they decide to include patients with missing data, they must decide how the data should be handled. In this study, we introduce various group-defining strategies (i.e., ITT, AT, and PP) in relation to this study example and explain how they can be used to address problems encountered.

Intention to treat (ITT)

The ITT principle is a group-defining strategy in which patients are maintained in the initial intervention group to which they were randomized and assigned, regardless of whether they actually received that intervention. With this approach, biases that can occur if some patients are noncompliant or nonadherent to protocols or excluded from the analyses are avoided. According to the ITT principle, all patients should be included in the group to which they are initially assigned as much as possible to preserve the essence of randomization, even if they do not receive the intended treatment, meet the inclusion criteria, or follow the study protocols.

Figs. 1B and 2B describe the ITT principle. Using this strategy, patients who did not receive the assigned treatment (SLIPA) (i.e., patients E and F) remain in the groups to which they were initially assigned (Figs. 1B and 2B). Similarly, patient K would be included in the intubation group, as initially assigned (Fig. 2B). Additionally, patients who did not meet the inclusion criteria (i.e., patient L) would be included in the analysis. Finally, even though some data were missing for certain patients (i.e., patients D and J), they were included in the analyses (Fig. 2B).

As such deviations from the study protocol can even occur in well-controlled clinical trials, they occur even more often in real-world scenarios. Therefore, it is more realistic to include pa-

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tients with such deviations in the analyses (ITT principle). Thus, using the ITT principle, the analysis of study data is as unbiased as possible. The Cochrane Collaboration also strongly recommends using the ITT principle and reporting results in clinical trials [8].

However, achieving the ITT principle in real-world settings is difficult. Therefore, a modified version of the ITT principle, called the modified ITT (mITT) principle, has been introduced. This approach allows for some deviations from the ideal ITT principle. For example, the mITT principle may only include patients who meet certain diagnostic criteria or receive standard treatments, or only those who have baseline assessments or are followed up for a certain length of time [9]. However, the definition of the mITT used in clinical trials is often inconsistent and arbitrary.

The statistical principles for clinical trials (ICH E9) guideline introduces the term "full analysis set" (FAS), which is also a type of mITT. The FAS is as complete and as close as possible to the ITT ideal of including all randomized subjects. These guidelines allow for the exclusion of subjects who fail major entry criteria, such as no applied treatment and no data available after randomization [10]. However, these major entry criteria are not commonly used to define the ITT principle [11].

As treated (AT)

The AT approach is a group-defining strategy in which patients are assigned to the analysis group according to the actual treatment received regardless of their randomization assignment [4,12]. This approach should be compared with the ITT principle, in which participants are analyzed according to their randomization assignments. In an ideal setting in which all participants receive their allocated treatments without errors, the results would be the same, though this is often not the case.

Figs. 1C and 2C show examples of the AT principle for participants who did not receive their randomly allocated treatments. In the study example, patients E and F were supposed to undergo an SLIPA insertion but underwent intubation instead (Figs. 1C and 2C), while patient K was supposed to undergo intubation but underwent an SLIPA insertion instead (Fig. 2C).

Using the ITT principle, participants who receive an intervention other than the randomly assigned intervention are analyzed according to their randomized assignments; thus, patients E and F were analyzed as part of the SLIPA group, and patient K was analyzed as part of the intubation group (Figs. 1B and 2B). However, when using the AT approach, participants who receive an intervention other than the randomly assigned intervention are analyzed based on the actual treatments received. Hence, in this case, patients E and F were analyzed as part of the intubation group, and patient K was analyzed as part of the SLIPA group (Figs. 1C and 2C).

Per protocol (PP)

Unlike the ITT principle, which considers only the randomized groups without excluding any subjects, and the AT approach, which considers only the actual treatments received without excluding subjects for noncompliance, nonadherence, or with missing data, the PP approach aims to confirm treatment effects under optimal conditions [13]. With the PP strategy, only subjects who meet the following criteria are included: 1) absence of major predefined protocol violations of the inclusion criteria, 2) completion of a pre-specified intervention, and 3) availability of data on the primary outcome [14].

Some subjects can be excluded from the study if the PP strategy is used. For example, patients with major predefined protocol violations in the inclusion criteria (e.g., patient L), those who do not follow the randomly assigned interventions (patients E, F, and K) (Figs. 1D and 2D), and those with missing data for the primary outcome (patients D and J) would be excluded (Fig. 2D). Consequently, only three patients in the SLIPA group (patients A, B, and C) and three patients in the intubation group (patients G, H, and I) would be included (Fig. 2D).

The PP approach is more likely to detect a difference between the experimental and control groups than the ITT principle because it only includes subjects who comply with or adhere to the study protocol without violations. This can lead to more significant differences between the groups. Researchers may be interested in detecting a treatment effect when compliance or adherence to the protocol is optimal, and the treatment effect based on the PP approach may be of greater interest to patients deciding whether to undergo a treatment.

The most critical aspect of using the PP approach is establishing clear subject inclusion or exclusion criteria during the study planning stage rather than during the analysis stage. If the study protocol is not accurately complied with or adhered to, the group that a subject belongs to may be ambiguous. Furthermore, specific reasons for excluding participants, such as the use of medications in the exclusion criteria, poor compliance or adherence, loss to follow-up, and missing data, should be predetermined. Additionally, researchers should carefully consider how excluding a subject for a specific reason may affect the study outcomes. This ensures that the analysis is unbiased and that any differences observed between the groups are attributable to the intervention itself rather than any methodological differences.

ITT vs. PP

In clinical trials, the AT and PP approaches can be difficult to interpret because the benefits of randomization (elimination of systematic errors in treatment assignment) are lost and thereby bias is introduced into the results [12]. This occurs when patients who adhere to their assigned treatments differ from those who do not adhere in ways that also affect outcomes. To address this issue, statistical techniques can be applied to account for potential variations among patients who do and do not adhere to their assigned treatments [4].

With the ITT principle, in which participants who do not receive their assigned interventions, are not compliant or adherent to protocols, or have missing data for the primary outcome are included, the estimated treatment effects may be diminished and diluted [15], generally moving the intervention effect size toward zero (Figs. 3A–D). If adherence to a treatment is linked to a greater treatment effect, the treatment effect predicted by the ITT-based approach is frequently smaller than the effect size assessed using the PP-based approach [16].

Thus, the ITT principle is often the preferred primary analysis approach because it is more conservative and less likely to uncover differences between groups in terms of superiority or inequality in RCTs (that seek to show investigational products as superior or unequal). In Figs. 3A and B, we see that in Case C, the null hypothesis can be rejected using the PP approach but not using the ITT approach. Therefore, a case that does not show a difference or superiority using the ITT approach will show a difference or superiority using PP.

However, in equivalence or non-inferiority trials (which seek to show equivalent or non-inferior treatment effects, respectively), diminishing and diluting the treatment effects of the ITT principle can result in the two treatment arms having similar outcomes [17]. In Figs. 3C and D, we see that in Case B, the null hypothesis cannot be rejected using PP but can be rejected using the ITT principle. Therefore, cases that do not show equivalence or non-inferiority with PP may show equivalence or non-inferiority with the ITT principle. However, this increased possibility of rejecting the null

Fig. 3. Comparison of treatment effects between the intention-to-treat (ITT) and per-protocol (PP) approaches. (A) Inequality trial, (B) superiority trial, (C) non-inferiority trial, and (D) equivalence trial. The white line represents the ITT approach, and the gray line represents the PP approach.

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hypothesis makes the ITT principle less conservative and can lead to inappropriate claims of equivalence or non-inferiority. In such cases, the PP may be more appropriate [18].

Similarly, when performing comparisons with placebo or sham groups, the ITT principle is the preferred group-defining strategy for primary analysis in superiority trials, which is the most common design for interventional studies. However, in equivalence or non-inferiority trials comparing a treatment with a placebo or sham group or in superiority or inequality trials comparing a treatment to an active drug, the application of the ITT principle is generally not conservative. Therefore, whether to use ITT must be considered carefully [19]. However, in most antibiotic non-inferiority trials, the ITT principle is more conservative than the PP approach [20]. This may be attributable to the lower treatment success rate, which contributes to a higher variance and wider CI using the ITT principle than using the PP, thus resulting in a lower CI limit. Consequently, although the PP is frequently recommended as the primary group-defining strategy for studies examining non-inferiority, serious concerns about its potential for informative censoring have been voiced.

Therefore, it is important to conduct analyses based on both the ITT principle and PP and to document all subjects who are included in the trial or excluded from the analyses [20]. The reasons for exclusion should be noted and the effects of all losses on the main analyses should be carefully considered. When both the ITT principle and the PP approach are used for analyzing the results of clinical trials and lead to similar conclusions, confidence in the trial results increases. Otherwise, efforts should be made to determine the cause of differences between the results. If the results from the PP approach demonstrate a more favorable treatment effect than those obtained using the ITT principle, this may suggest that participants adhering to and/or complying with the treatment had better results. A high dropout rate or missing data may dilute the treatment effect from the ITT principle because this approach incorporates all participants, even those with incomplete data. Substantial differences between the results obtained from the ITT principle and PP approach may imply difficulties in the generalizability of the treatment to real-world settings.

Therefore, the CONSORT guidelines also strongly suggest that estimates from both the ITT and PP approaches be provided in trial reports [21]. However, excluding a significant proportion of subjects from the PP approach may raise questions about the overall validity of the trial.

Missing data

Missing data can arise due to the attrition or exclusion of participants from the study. Attrition occurs when the participants are lost to follow-up, withdraw from the study, or fail to provide adequate data. Exclusion occurs when a participant does not meet the study inclusion criteria or is excluded for other reasons during the course of the study. Missing data can lead to various problems including a reduction in statistical power, bias in parameter estimation, reduced sample representativeness, and complications in study analysis. These distortions can threaten the validity of the trial and lead to invalid conclusions [22].

Missing data is typically handled using statistical methods such as complete case analysis or list-wise deletion (i.e., ignoring, deleting, or analyzing data from incomplete subjects with missing data) or imputation (i.e., substituting some value for the missing data and performing analyses using the imputed value) or analyzing incomplete data using methods that do not require a complete dataset (i.e., likelihood-based methods, moment-based methods, and semi-parametric models for survival data). In addition, researchers can perform sensitivity analyses to evaluate the robustness of the results when applying various statistical methods or assumptions.

The choice of method depends on the primary group-defining strategy used for the primary outcome. For example, investigators may perform a complete case analysis with the PP approach or impute missing data for mITT analyses because with this approach, patients with missing data must be included.

Additionally, when researchers calculate sample sizes for their studies, they should consider the primary group-defining strategy. If they plan to use the ITT principle, their estimates of the effect size should be adjusted compared to the PP approach because the ITT principle includes data from non-compliant or non-adherent patients, those lost to follow-up, and those with missing data, which can reduce effect size estimates. The variability in adjusting the effect size estimate should also be considered. Additionally, when calculating sample sizes, researchers should consider dropout, non-compliance, or non-adherence rates, depending on whether the missing data will be included and/or imputed.

Conclusion

There are various group-defining strategies for analyzing RCT data, including the ITT, AT, and PP approaches. The ITT principle aims to replicate real-world clinical settings, where many anticipated or unexpected events may occur that diverge from the study protocol. The PP approach, on the other hand, aims to confirm the treatment effects under optimal conditions.

In general, when comparing treatments to placebo or sham groups, the ITT principle is preferred for superiority or inequality

trials, whereas the PP approach is preferred for equivalence or non-inferiority trials. However, analyses based on both the ITT principle and PP approach should be conducted, the results should be compared, and differences should be analyzed.

If research is conducted under ideal conditions without any non-compliance, non-adherence, or missing data, all datasets based on the ITT, AT, and PP approaches would be identical. However, deviations from ideal conditions in real-world settings are common. Hence, researchers should anticipate and account for these potential deviations during the planning stage and make decisions in advance regarding how to handle and incorporate such deviations into the resulting data. Overall, performing analyses using both the ITT principle and PP approach can provide a more complete picture of the treatment effects and help ensure the reliability of trial results.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

This is a statistical round article about methodology of the research. Therefore, the data availability is not applicable.

Author Contributions

EunJin Ahn (Methodology; Validation; Writing – original draft; Writing – review & editing)
Hyun Kang (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)

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Predicting optimal endotracheal tube size and depth in pediatric patients using demographic data and machine learning techniques

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Background: Use of endotracheal tubes (ETTs) with appropriate size and depth can help minimize intubation-related complications in pediatric patients. Existing age-based formulae for selecting the optimal ETT size present several inaccuracies. We developed a machine learning model that predicts the optimal size and depth of ETTs in pediatric patients using demographic data, enabling clinical applications.

Methods: Data from 37,057 patients younger than 12 years who underwent general anesthesia with endotracheal intubation were retrospectively analyzed. Gradient boosted regression tree (GBRT) model was developed and compared with traditional age-based formulae.

Results: The GBRT model demonstrated the highest macro-averaged F1 scores of 0.502 (95% CI [0.486, 0.568]) and 0.669 (95% CI [0.640, 0.694]) for predicting the uncuffed and cuffed ETT size (internal diameter), outperforming the age-based formulae that yielded 0.163 (95% CI [0.140, 0.196], P < 0.001) and 0.392 (95% CI [0.378, 0.406], P < 0.001), respectively. In predicting the ETT depth (distance from tip to lip corner), the GBRT model showed the lowest mean absolute error of 0.71 cm (95% CI [0.69, 0.72]) and 0.72 cm (95% CI [0.70, 0.74]) compared to the age-based formulae that showed an error of 1.18 cm (95% CI [1.16, 1.20], P < 0.001) and 1.34 cm (95% CI [1.31, 1.38], P < 0.001) for uncuffed and cuffed ETT, respectively.

Conclusions: The GBRT model using only demographic data accurately predicted the ETT size and depth. If these results are validated, the model may be practical for predicting optimal ETT size and depth for pediatric patients.

Keywords: Airway management; Demography; General anesthesia; Intratracheal intubation; Machine learning; Pediatrics.

Introduction

Selecting an appropriate size and depth of the endotracheal tube (ETT) is essential to minimize intubation-related complications in pediatric patients. An improper ETT size may require reintubation, increasing the risk of airway injury and prolonged apnea [1–3]. Moreover, inaccurate estimation of tube depth can cause bronchial intubation that can result in pneumothorax or atelectasis. By contrast, shallow insertion of an ETT can lead to an unsecured airway or inadequate ventilation [4].

Several methods have been proposed to select the optimal ETT size. Among those, Cole's age-based formula is typically used in clinical practice to estimate the internal diameter (ID) of uncuffed ETTs [5]. Other age-based formulae, such as those proposed by Khine et al. [6] and Duracher et al. [7], have been suggested for cuffed ETTs. The age-based formulae have also been used to estimate the optimal depth of ETT insertion [8]. However, several inaccuracies have been reported in these age-based formulae [9–11]. These inaccuracies might be because of the nonlinearity of tracheal growth with age. Another possible reason is inter-individual discrepancies in ETT size among individuals of the same age [12–14].

Machine learning algorithms handling complex nonlinear relationships have shown excellent performance in various medical fields [15]. However, few studies have integrated machine learning models to suggest the optimal ETT size and depth for pediatric patients [16]. Zhou et al. [16] implemented machine learning techniques with image-based features such as tracheal diameter at the C6, C7, and T2 levels or the distance from C6 to the tracheal carina. However, their model requires manual measurements by clinicians using X-ray images that are not usually available for pediatric surgical patients. By contrast, basic demographic data, such as age, sex, weight, and height, can be easily acquired from the most recent electronic health record system.

In this study, we aimed to develop and validate an explainable machine learning model to predict the optimal ETT size and depth for pediatric patients using only demographic data. Our hypothesis was that the machine learning model would outperform traditional age-based formulae in predicting the optimal ETT size and depth. A favorable model developed through this approach may be beneficial in routine anesthesia practice.

Materials and Methods

The Institutional Review Board of Seoul National University Hospital (Approval number: 2304-012-1418) approved this study and waived the requirement for informed consent owing to the retrospective nature of the study design. We followed the recommendations of the 'Strengthening the Reporting of Observational Studies in Epidemiology' guidelines [17].

Study population

Data were collected from 151,651 pediatric surgical patients who underwent general anesthesia with endotracheal intubation at Seoul National University Hospital from October 2004 to November 2022. Cases with the following characteristics were excluded: (1) age > 12 years; (2) specialized ETT type, such as right angle endotracheal, double lumen, and electromyogram tubes; (3) missing values for ETT type and size in the anesthesia note; and (4) surgical cases of second or subsequent surgeries for a single patient.

Data collection

Nursing and anesthesia notes were extracted from the hospital's clinical data warehouse. The most recent values of sex, height, and weight before surgery were extracted from the nursing notes. The ETTs utilized throughout the study period were Shiley™ Oral/Nasal Endotracheal Tube Cuffless Murphy Eye (Medtronic, Ireland) or Shiley™ Hi-Lo Oral/Nasal Tracheal Tube (Medtronic, Ireland). The type, size (ID), and fixed depth (distance from tip to lip corner) of the ETT were identified from the anesthesia notes.

A routine practice during the study at our hospital was selecting the ETT size based on Cole's formula, as decided by the attending anesthetists. If ventilation was inadequate owing to a leak, the patient was reintubated with a larger ETT. By contrast, if the tube size was large and did not advance within the trachea, a smaller size was retried. The optimal tube depth was determined by auscultation. After tracheal intubation, the ETT was introduced until the right upper lobe breath sounds disappeared. Subsequently, the tube was withdrawn until the upper lobe breath sounds reappeared. An additional length (1–2 cm) was retracted to prevent bronchial intubation by position change. Once fixed, the presence of breath sounds from both lung fields was reconfirmed, and the depth marker at the lip corner was recorded in the anesthesia note. The ID and depth of the ETT were recorded as 0.5 mm and 0.5 cm, respectively.

Model development

We developed regression models using gradient boosted regression tree (GBRT) and linear regression (LR) to predict the size and depth of the ETT separately. Due to the distinct rationale behind tube selection, we trained separate models to predict the size and depth of uncuffed and cuffed ETTs. Statistical outliers (± 2SD [standard deviation]) for height, weight, tube size, and depth within one-year intervals were considered as missing values. We performed multiple imputations to substitute the missing height and weight values.

The most recent 20% of the data was designated as the test dataset. The remaining data were assigned as the training dataset, separately for uncuffed and cuffed ETT types, to train the models. The test dataset was used to evaluate and compare the perfor-

mances with that of the traditional formulae. Subsequently, we used the BorutaSHAP method to select the necessary input variables from demographic data (age, sex, height, and weight) in the GBRT model. This method combines the Boruta feature selection algorithm with the Shapley value calculations [18]. After selecting the most relevant variables, they were incorporated into the final input of the machine learning models to predict the ID and fixed depth of the ETT. The hyperparameters for the GBRT model were determined using ten-fold cross-validation, and a grid search was performed for each combination of the hyperparameters. Supplementary Table 1 lists the hyperparameter combinations.

Outcome variables

The ETT size predicted by the models was rounded to the nearest 0.5 mm. The primary outcome for the size model was the macro-averaged F1 score that comprehensively evaluates the model's performance across all classes by calculating the unweighted mean value of the F1 score for each class. Additionally, we computed the accuracy of predicting the exact size and the size within 0.5 mm of the tube, given that clinicians typically prepare three sizes of ETTs in case of failure.

To compare the performance of our model in predicting the size of an ETT, we selected Cole's formula [5] for an uncuffed ETT (ID [mm] = age in years / 4 + 4.0) and Duracher's formula [7] for a cuffed ETT (ID [mm] = age in years / 4 + 3.5) as traditional age-based formulae. For below one year of age, an ID of 3.5 mm was used, and for between one and two years of age, 4.0 mm was used for the uncuffed ETT, as Cole's formula applies over the age of two. A size smaller by one was used for cuffed ETTs for ages less than two years. The Penlington's formula (ID [mm] = age in years / 4 + 4.5) was also used to estimate the uncuffed ETT size [19].

The primary outcome of the depth model was measured in terms of the mean absolute error (MAE). Additionally, root mean squared error (RMSE) and R-squared were calculated to evaluate the performance of the depth model. To calculate the depth of the ETT, we selected traditional age-based formulae based on the Pediatric Advanced Life Support (PALS) guidelines (recommended depth of insertion [cm] = age in years / 2 + 12) [8]. We compared the performance of the GBRT models with that of traditional age-based formulae and LR models.

The linearity assumptions in the relationships between ETT size and depth with age were tested by verifying the normality of the residual distributions at a significance level of 0.05. The scatter plots of these variables and those of the residuals and fitted values were depicted to verify the linear relationship.

We adopted the Shapley additive explanation (SHAP) method to enhance the interpretability of the machine learning model. This method calculates the contribution of the input variables to the prediction and quantifies how each variable affects the output of the machine learning model [20].

To enhance the limited intuitive understanding of machine learning outcomes, we constructed a table presenting predictions for tube size using the GBRT model. This table was created by referencing the pediatric growth chart offered by the Korea Disease Control and Prevention Agency [21]. We incorporated weight and height data corresponding to the 5th, 15th, 25th, 50th, 75th, 85th, and 95th percentiles for each age from the pediatric growth chart.

We have released our data, model parameters, and code in a public repository (https://github.com/Hyeonsik/ endotracheal_tube.git) and developed a web-based calculator (https://tubesize.net) to validate and apply the results.

Subgroup analysis

We performed a subgroup analysis of our predictive model for ETT size according to age. The patient population was stratified into three distinct age groups: neonates (< 1 month), infants (< 1 year), and others (≥ 1 year). Subsequently, we assessed and compared the predictive performance with the trained GBRT model within these subgroups without retraining.

Statistical analysis

Continuous variables, such as age, weight, and height, are presented as means (standard deviation) or medians (Q1, Q3), depending on the results of the Shapiro–Wilk test. Categorical variables, such as sex and ETT type, are presented numerically (percentages). Model performances were computed with a 95% CI through bootstrapping methods, and ml-stat-util (https://github.com/mateuszbuda/ml-stat-util) was employed for conducting statistical tests. The Mood's median test was performed for model comparisons in the subgroup analysis. The Mann-Whitney *U* test or two-sample t-test was performed to compare continuous variables depending on the Shapiro–Wilk test results. For the comparison of categorical variables, the chi-square test was performed. Considering the two outcomes (size and depth) and two tube types (cuffed and uncuffed), a P value < 0.0125 was considered statistically significant after the Bonferroni correction.

A custom program was developed using Python® (Python Software Foundation, USA) with scikit-learn 1.0.2, XGBoost 1.7.3, Keras 2.7.0, SHAP 0.41.0, BorutaSHAP 1.1, and stat-util libraries,

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to develop and validate the model.

Results

After excluding 114,594 patients, the final analysis included 37,057 surgical procedures (Fig. 1). The general characteristics of the data are summarized in Table 1. There were differences in age, height, weight, and the distribution of tube depth between training and test sets for both cuffed and uncuffed ETT data. The BorutaSHAP method was employed to identify significant input variables for the size and depth models, and the variable 'sex' was removed, except for the model predicting the depth of uncuffed ETTs, as they did not significantly affect the output ($P < 0.05$, Fig. 2). The results showed that age, weight, and height are critical factors in predicting ETT size and cuffed ETT depth. By contrast, age, sex, weight, and height are critical factors in predicting uncuffed ETT depth. Scatter plots depicting ETT size and depth by age and scatter plots depicting the residuals and fitted values are

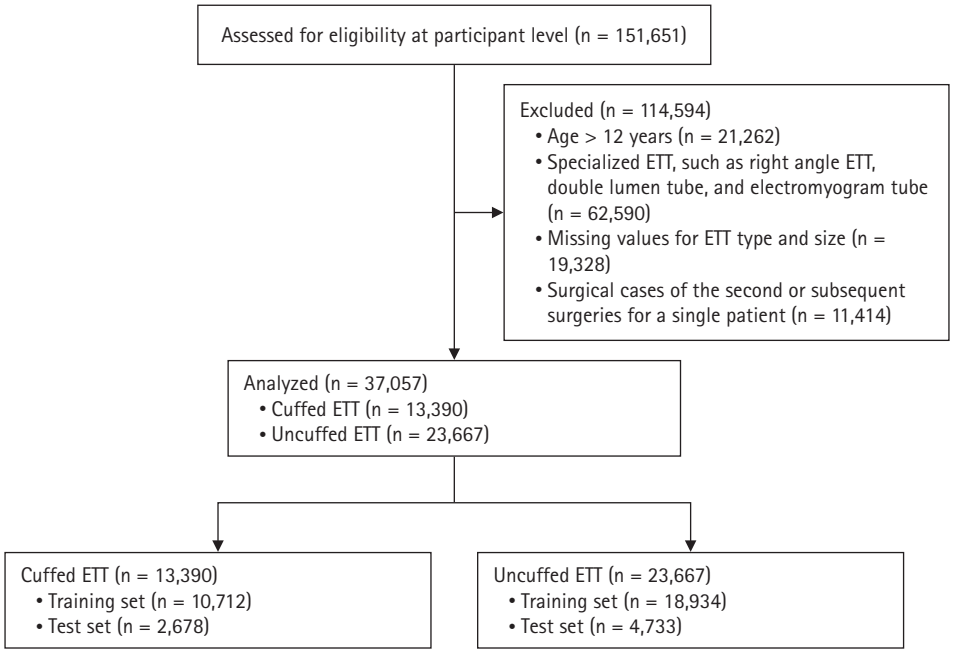

Fig. 1. Study flowchart. ETT: endotracheal tube.

Table 1. Comparison of Demographic and Tube Data between Training and Test Datasets for Cuffed and Uncuffed ETTs in This Study

Variable	Missing (%)	Training dataset	Test dataset	P value
Uncuffed ETT		18,934 (80.0)	4,733 (20.0)	
Age (yr)	0	3.32 (0.88, 5.41)	2.94 (0.91, 4.75)	< 0.001
Sex (M)	0	11,122 (58.7)	2,735 (57.8)	0.239
Height (cm)	6.6	92.2 (74.2, 111.0)	90.1 (75.0, 107.0)	< 0.001
Weight (kg)	2.7	14.6 (9.0, 19.0)	13.7 (9.2, 17.7)	< 0.001
ID of ETT (mm)	0	4.8 (4.0, 5.5)	4.8 (4.0, 5.5)	0.867
Fixed depth (cm)	10.9	13.6 (12.0, 15.5)	13.2 (11.5, 15.0)	< 0.001
Cuffed ETT		10,712 (80.0)	2,678 (20.0)	
Age (yr)	0	7.28 (3.22, 10.9)	4.36 (0.539, 7.56)	< 0.001
Sex (M)	0	6,403 (59.8)	1,528 (57.1)	0.011
Height (cm)	3.9	120.0 (96.0, 144.1)	97.6 (67.0, 125.4)	< 0.001
Weight (kg)	2.9	28.4 (14.5, 39.5)	18.6 (7.5, 25.4)	< 0.001
ID of ETT (mm)	0	5.3 (4.5, 6.0)	4.5 (3.5, 5.5)	< 0.001
Fixed depth (cm)	9.6	16.2 (14.0, 19.0)	14.1 (11.0, 17.0)	< 0.001

Values are presented as mean ± SD, median (Q1, Q3), or number (proportion). ETT: endotracheal tube, ID: internal diameter.

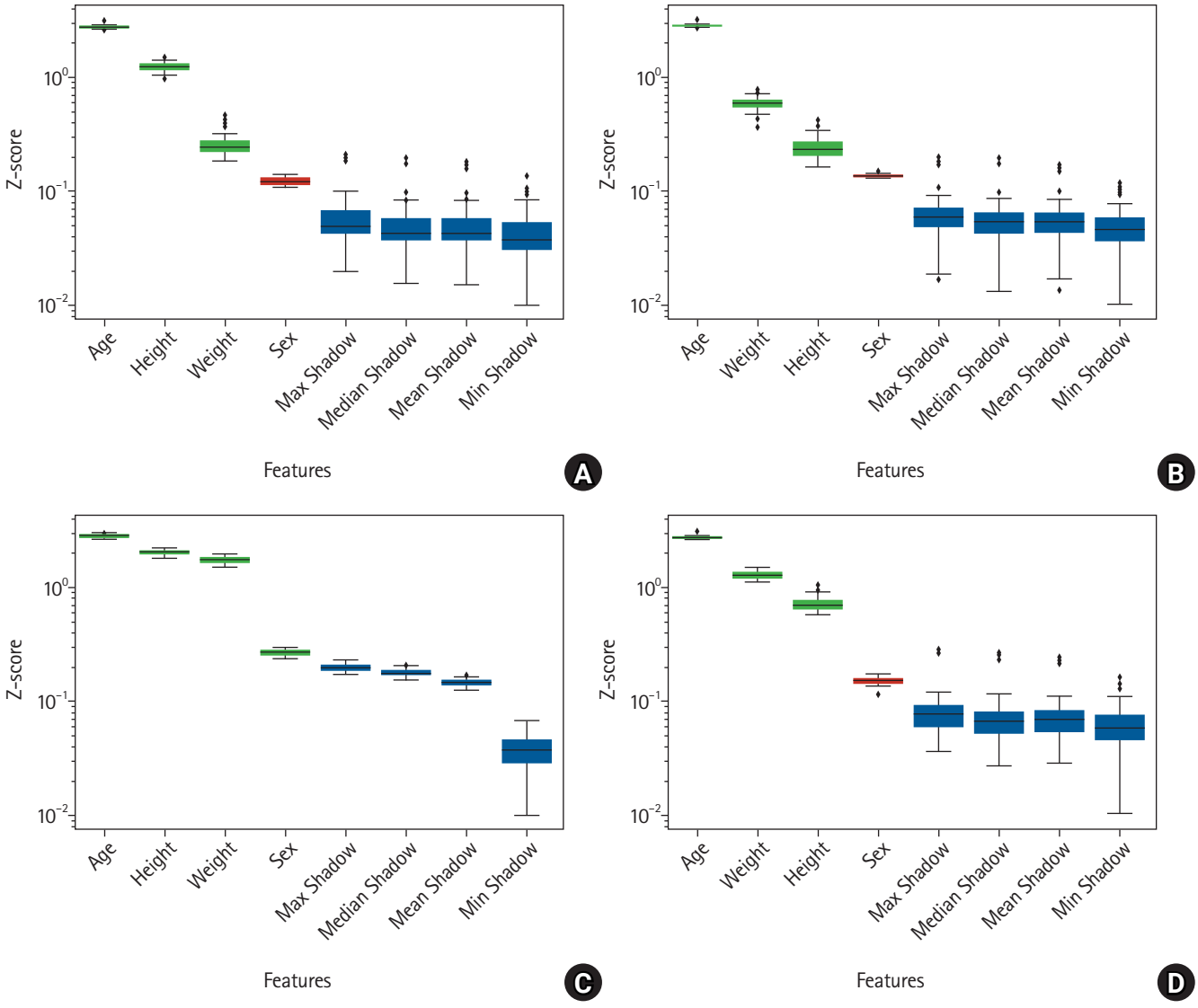

Fig. 2. Boxplot of the feature importance from input candidates using the BorutaSHAP method. (A) Boxplot of the feature importance from input candidates (age, sex, weight, height, and existence of cuff) for predicting uncuffed ETT size using the BorutaSHAP method. (B) Boxplot of the feature importance from input candidates (age, sex, weight, height, and existence of cuff) for predicting cuffed ETT size using the BorutaSHAP method. (C) Boxplot of the feature importance from input candidates (age, sex, weight, height, and existence of cuff) for predicting uncuffed ETT depth using the BorutaSHAP method. (D) Boxplot of the feature importance from input candidates (age, sex, weight, height, and existence of cuff) for predicting cuffed ETT depth using the BorutaSHAP method. X-axis presents the input features and Y-axis shows the Z-score of whether each feature has an importance significantly lower than the threshold. Features confirmed important are presented in green ($P < 0.05$) and blue colors, while red color represents unimportant features ($P < 0.05$). The term 'Shadow' on the X-axis refers to shadow features generated by randomly permuting the dataset of each original feature. Then, the feature importance are computed in the original and the generated shadow features. ETT: endotracheal tube.

shown in Fig. 3. The linearity assumption between ETT size and age was not achieved ($P < 0.001$).

The GBRT model showed the highest macro-averaged F1 score of 0.502 (95% CI [0.486, 0.568]) in predicting the size of uncuffed ETTs and 0.669 (95% CI [0.640, 0.694]) for cuffed ETTs. This performance was superior to that of traditional age-based formulae that achieved a macro-averaged F1 score of 0.163 (95% CI [0.140, 0.196], $P < 0.001$) for uncuffed ETTs and 0.392 (95% CI [0.378, 0.406], $P < 0.001$) for cuffed ETTs (Table 2).

The GBRT model achieved the best performance in predicting the ETT depth, with an MAE of 0.71 cm (95% CI [0.69, 0.72]) for uncuffed ETTs and 0.72 cm (95% CI [0.70, 0.75]) for cuffed ETTs. The GBRT model outperformed the traditional age-based formula (MAE for uncuffed ETTs = 1.18 cm [95% CI 1.16, 1.20], MAE

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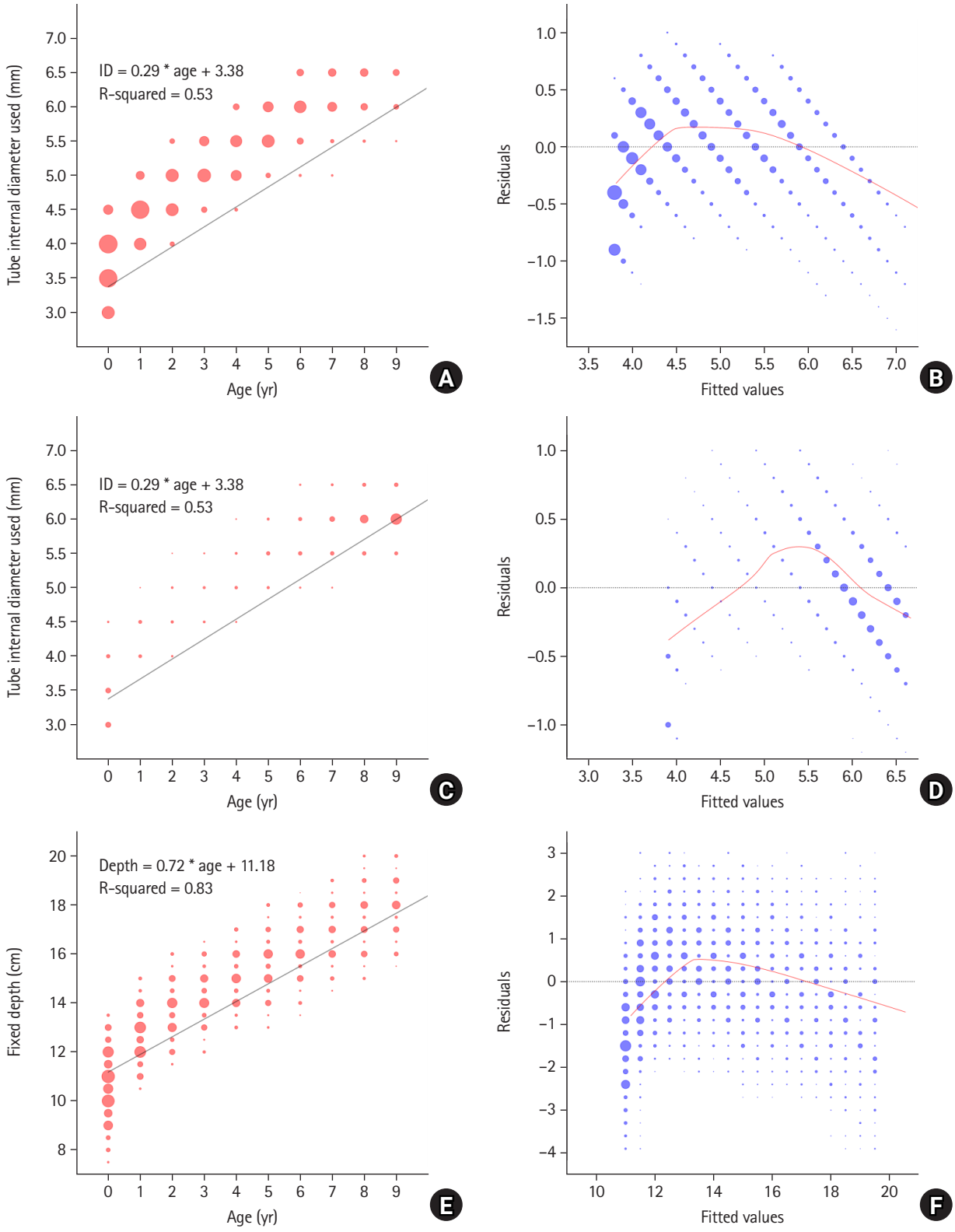

Fig. 3. Scatter plots and residuals analysis for ETT size and depth by age. (A) Scatter plot of uncuffed ETT size by age. (B) Scatter plot of residuals for LR analysis between uncuffed ETT size and age. X-axis presents residuals that indicate the difference between the observed and predicted ETT sizes. Y-axis presents the fitted values generated using a LR model. (C) Scatter plot of cuffed ETT size according to age. (D) Scatter plot of residuals and fitted values for uncuffed ETT size by age. (E) Scatter plot of ETT depth by age. (F) Scatter plot of residuals and fitted values for ETT depth according to age. The black line refers to the LR trend between two axes, and red line refers to a locally weighted scatterplot smoother fitted to the residual scatter plot. ETT: endotracheal tube, LR: linear regression.

Table 2. Performance of GBRT Model, MLR Model, and Age-based Formulae for Predicting the Size of ETT

Model	Macro-averaged F1	P value	Accuracy within 0.5 mm (%)	P value	Accuracy (%)	P value
Uncuffed ETT						
GBRT	0.502 (0.486, 0.568)	Reference	98.1 (97.8, 98.4)	Reference	58.2 (57.0, 59.4)	Reference
MLR	0.407 (0.395, 0.424)	< 0.001	97.2 (96.8, 97.6)	< 0.001	53.8 (52.5, 55.0)	< 0.001
Penlington's*	0.203 (0.196, 0.211)	< 0.001	82.6 (81.7, 83.5)	< 0.001	41.3 (40.2, 42.5)	< 0.001
Cole's†	0.163 (0.140, 0.196)	< 0.001	78.1 (77.1, 79.1)	< 0.001	20.3 (19.3, 21.2)	< 0.001
Cuffed ETT						
GBRT	0.669 (0.640, 0.694)	Reference	99.5 (99.3, 99.7)	Reference	70.1 (68.6, 71.5)	Reference
MLR	0.576 (0.551, 0.600)	< 0.001	99.4 (99.1, 99.6)	0.589	58.4 (56.8, 59.9)	< 0.001
Duracher's‡	0.392 (0.378, 0.406)	< 0.001	96.6 (96.0, 97.2)	< 0.001	46.9 (45.3, 48.5)	< 0.001

Values are presented as numbers (95% CI). GBRT: gradient boosted regression tree, MLR: multiple linear regression, ETT: endotracheal tube, ID: internal diameter. *Penlington's formula (ID of the uncuffed ETT [mm] = age in years / 4 + 4.5), †Cole's formula (ID of the uncuffed ETT [mm] = age in years / 4 + 4.0), ‡Duracher's formula (ID of the cuffed ETT [mm] = age in years / 4 + 3.5).

Table 3. Performance of GBRT, MLR Models, and Age-based Formula for Predicting the Depth of ETT

Model	MAE (cm)	P value	RMSE (cm)	P value	R-squared	P value
Uncuffed ETT						
GBRT	0.71 (0.69, 0.72)	Reference	0.88 (0.87, 0.90)	Reference	0.831 (0.823, 0.839)	Reference
MLR	0.74 (0.73, 0.76)	< 0.001	0.94 (0.92, 0.96)	< 0.001	0.803 (0.793, 0.812)	< 0.001
PALS*	1.18 (1.16, 1.20)	< 0.001	1.46 (1.44, 1.49)	< 0.001	0.572 (0.554, 0.589)	< 0.001
Cuffed ETT						
GBRT	0.72 (0.70, 0.74)	Reference	1.00 (0.91, 1.14)	Reference	0.904 (0.875, 0.921)	Reference
MLR	0.77 (0.75, 0.80)	< 0.001	1.05 (0.97, 1.20)	< 0.001	0.884 (0.852, 0.903)	< 0.001
PALS	1.34 (1.31, 1.38)	< 0.001	1.67 (1.61, 1.75)	< 0.001	0.720 (0.693, 0.740)	< 0.001

Values are presented as numbers (95% CI). GBRT: gradient boosted regression tree, MLR: multiple linear regression, ETT: endotracheal tube, MAE: mean absolute error, RMSE: root mean squared error, PALS: pediatric advanced life support. *PALS guideline (depth of insertion [cm] = age in years / 2 + 12).

for cuffed ETTs = 1.34 cm [95% CI 1.31, 1.38]). There was a significant performance difference between the GBRT model and the traditional age-based formula (P < 0.001) (Table 3).

In the subgroup analysis, the size model showed the highest macro-averaged F1 score in the infant group for uncuffed ETTs and the other groups for cuffed ETTs, while the other groups showed the lowest accuracy for both uncuffed and cuffed ETT sizing (Table 4).

The tube sizes and depths predicted by the GBRT model for the representative demographic values are presented in Supplementary Table 2.

The SHAP summary plot in Supplementary Fig. 1 illustrates the contribution of each input variable to the output of the GBRT model. Older age, uncuffed ETT, heavier weight, and taller height contributed to larger ETT size. Older age, heavier weight, taller height, and male sex were associated with deeper ETT depth. The SHAP dependence plots presented in Supplementary Fig. 2 and Supplementary Fig. 3 illustrate the effect of each input variable on the prediction.

Discussion

In this study, we developed and validated machine learning models to predict the optimal ETT size and depth in pediatric patients. Our models used only demographic variables and considered the GBRT algorithm. The developed models outperformed the traditional age-based formulae.

Previous studies on optimal ETT size using age-based formulae have reported an accuracy in the range of 15%–50% in predicting the exact uncuffed or cuffed ETT size [9,10,14,16]. However, our model exhibited an accuracy of 58.2% and 70.1% for exact matching and 98.1% and 99.5% for an accuracy within 0.5 mm for uncuffed and cuffed ETTs, respectively. The differences in performance might be attributable to the use of machine learning algorithms that can model nonlinear relationships. The linearity test results and SHAP dependency plot in our study

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Table 4. Subgroup Analyses based on Age for Predicting ETT Size using GBRT Model

	Macro-averaged F1	P value	Accuracy within 0.5 mm (%)	P value	Accuracy (%)	P value
Uncuffed ETT						
Neonate	0.371 (0.300, 0.467)	< 0.001	98.2 (96.3, 99.4)	< 0.001	65.0 (58.9, 71.2)	< 0.001
Infant	0.521 (0.500, 0.543)	< 0.001	98.6 (98.0, 99.2)	< 0.001	65.7 (63.3, 67.9)	< 0.001
Others	0.426 (0.389, 0.480)	Reference	97.9 (97.5, 98.3)	Reference	55.5 (54.1, 56.9)	Reference
Cuffed ETT						
Neonate	0.541 (0.459, 0.674)	< 0.001	100.0 (100.0, 100.0)	< 0.001	88.3 (83.0, 93.6)	< 0.001
Infant	0.510 (0.429, 0.632)	< 0.001	99.6 (99.3, 99.9)	< 0.001	82.4 (80.2, 84.6)	< 0.001
Others	0.626 (0.591, 0.657)	Reference	99.4 (99.0, 99.7)	Reference	63.1 (61.2, 65.0)	Reference

Values are presented as numbers (95% CI). ETT: endotracheal tube, GBRT: gradient boosted regression tree.

confirmed the nonlinear relationship between the size or depth of the ETT and age.

Other demographic variables, such as height and weight, also contributed significantly to improving the prediction of ETT size and depth. In the analysis based on the BorutaSHAP method, all variables, except for sex, were included in the GBRT model for predicting the ETT size. Therefore, adding these variables significantly improves model performance. These results are consistent with previous findings stating that there was no difference in terms of sex in developing the trachea throughout childhood [22]. Moreover, sex was only included in the GBRT model for predicting the depth of uncuffed ETTs. The uncuffed tube depth may be affected by sex owing to the difference in tongue size, as the ETT depth was measured at the lip corner.

In a previous study, Zhou et al. [16] developed machine learning models using demographic data and extracted features from the chest X-ray images of 990 patients to estimate the ETT size. The accuracies of their models were 57.5% and 52.3% for cuffed and uncuffed ETTs, respectively, whereas our model using only demographic data yielded accuracies of 70.1% and 58.2%, respectively. This difference can be attributed to the massive volume of data we used that was 25 times more than that used by Zhou et al.

Although Cole's formula has been used in clinical practice for several decades, several studies have reported that Penlington's formula is more accurate for predicting uncuffed ETT size [10,16]. Our study also found that Penlington's formula that suggests a larger ETT size was more accurate than Cole's formula in predicting uncuffed ETTs in pediatric patients. This difference in accuracy may be attributed to variations in the growth curve in pediatric populations over time and race since Cole's formula was first introduced in a North American pediatric population in 1957 [5]. Nevertheless, all age-based formulae investigated in this study were highly inaccurate compared to the machine learning models.

In our subgroup analysis, the accuracy of the 'others' group, consisting of individuals aged one year or older, in predicting the ETT size was the lowest among the three age groups. This may be because the trachea size in the neonate and infant groups was relatively uniform compared to those in the other age groups. The difference in performance among the age groups also indicated a nonlinear relationship between age and tube size.

The strength of our model is its readiness in clinical situations because it is available as a web calculator, and its code is available online. In most electronic medical record systems, height and weight information is obtained before surgery. Additionally, according to the BorutaSHAP results obtained in this study, this additional information is significant. Therefore, a system implemented with the proposed model to provide automated suggestions could be practical for determining a more accurate ETT size and fixation depth in pediatric patients.

Our study has a few limitations. First, because our study was retrospective, there may be inevitable biases, and the excluded or missing data could have affected the results. Therefore, future prospective validation is needed to address these issues with minimal data loss. Second, the generalizability of our study may be limited because it was conducted for an Asian population at a single institute. The different patterns in clinical practices may influence the machine learning model's performance and limit its real-world applicability. Therefore, conducting external validation studies across multiple centers, encompassing diverse patient populations and clinical practices, is crucial to assess the robustness and reliability of the model's performance before the application. Third, we might have missed some important input variables, such as congenital diseases that may further affect airway anatomy and result in size depth variations of the ETT [23,24]. Fourth, different cuff designs, such as Hi-Contour or TaperGuard™ (Medtronic, Ireland), could result in variations in the optimal tube size and depth. Therefore, the models may require retraining before applying them to different tube types using the corresponding data for

each specific tube type. Fifth, although we utilized the minimal set of readily collectible demographic variables, additional input parameters, such as Mallampati classification or imaging data like X-rays and ultrasound images, can improve model performance. Sixth, the labeled ETT size and depth may not be optimal because there could be some tolerance for improper tube size and depth by the attending anesthetist based on auscultation. Additionally, there may be inaccuracies in the recorded tube depth because the fixed depth difference may be changed by the patient's position, especially in neonates and infants.

In conclusion, we developed and validated an explainable machine learning model to precisely estimate the size and depth of an ETT in pediatric patients using only basic demographic data. Prospective validation is warranted to validate our results before integration into clinical practice.

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Conflicts of Interest

Hyung-Chul Lee was an Editor for the Korean Journal of Anesthesiology from 2020 to 2022. However, he was not involved in any process of review for this article, including peer reviewer selection, evaluation, or decision-making. There were no other potential conflicts of interest relevant to this article.

Data Availability

The datasets generated during and/or analyzed during the current study are available in the github repository (https://github.com/Hyeonsik/endotracheal_tube).

Author Contributions

Hyeonsik Kim (Data curation; Formal analysis; Software; Writing – original draft)
Hyun-Kyu Yoon (Conceptualization; Supervision)
Hyeonhoon Lee (Formal analysis; Software)
Chul-Woo Jung (Conceptualization; Writing – review & editing)
Hyung-Chul Lee (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Supervision)

Supplementary Materials

Supplementary Table 1. Combinations of hyperparameters for the gradient boosted regression tree (GBRT) model predicting size and depth of endotracheal tube (ETT).
Supplementary Table 2. The predicted internal diameter (ID) and depth of the endotracheal tubes (ETTs) using the gradient boosted regression tree (GBRT) models based on the representative demographic values.
Supplementary Fig. 1. Shapley additive explanation summary plot for endotracheal tube (ETT) size and depth prediction by gradient boosted regression tree (GBRT) models. (A) Shapley additive explanation summary plot for input variables in the GBRT model for predicting the size of uncuffed ETTs. (B) Shapley additive explanation summary plot for input variables in the GBRT model for predicting the size of cuffed ETTs. (C) Shapley additive explanation summary plot for input variables in the GBRT model for predicting the depth of uncuffed ETTs. (D) Shapley additive explanation summary plot for input variables in the GBRT model for predicting the depth of cuffed ETTs. The red and blue dots represent the higher and lower values of the variables, respectively. Large Shapley values indicate a high contribution to output regardless of positive or negative. Older age, heavier weight, and taller height contribute to a larger size of the ETT. Older age, heavier weight, taller height, and male sex were associated with deeper ETT depth.
Supplementary Fig. 2. Shapley additive explanation dependence plot for each input variable in the gradient boosted regression tree (GBRT) model for predicting the size of uncuffed endotracheal tubes (ETTs): (A) age, (B) weight, and (C) height. Shapley additive explanation dependence plot for each input variable in the GBRT model for predicting the size of cuffed ETTs: (D) age, (E) weight, and (F) height. Effect of a feature on the model's output and the distribution of the feature's value is visualized as a scatter plot in the Shapley dependence plot. Horizontal axis represents the value of each feature, and the vertical axis represents the Shapley values of a feature. The light grey area at the base of the plot represents a histogram displaying the distribution of data values.
Supplementary Fig. 3. Shapley additive explanation dependence plot for each input variable in the gradient boosted regression tree (GBRT) model for predicting the depth of uncuffed ETTs: (A) age, (B) sex, (C) weight, and (D) height. Shapley additive explanation dependence plot for each input variable in the GBRT model for predicting the depth of cuffed ETTs: (E) age, (F) weight, and (G) height. Effect of a feature on the model's output and the distribution of the feature's value is visualized as a scatter plot in the Shapley dependence plot. The horizontal axis represents the value

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of each feature, and the vertical axis represents the Shapley values of a feature. The light grey area at the base of the plot represents a histogram displaying the distribution of data values.

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Association between inflammation-based prognostic markers and mortality of non-cardiac surgery

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Background: To evaluate the association between inflammation and nutrition-based biomarkers and postoperative outcomes after non-cardiac surgery.
Methods: Between January 2011 and June 2019, a total of 102,052 patients undergoing non-cardiac surgery were evaluated, with C-reactive protein (CRP), albumin, and complete blood count measured within six months before surgery. We assessed their CRP-to-albumin ratio (CAR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and modified Glasgow Prognostic Score (mGPS). We determined the best cut-off values by using the receiver operating characteristic (ROC) curves. Patients were divided into high and low groups according to the estimated threshold, and we compared the one-year mortality.
Results: The one-year mortality of the entire sample was 4.2%. ROC analysis revealed areas under the curve of 0.796, 0.743, 0.670, and 0.708 for CAR, NLR, PLR, and mGPS, respectively. According to the estimated threshold, high CAR, NLR, PLR, and mGPS were associated with increased one-year mortality (1.7% vs. 11.7%, hazard ratio [HR]: 2.38, 95% CI [2.05, 2.76], P < 0.001 for CAR; 2.2% vs. 10.3%, HR: 1.81, 95% CI [1.62, 2.03], P < 0.001 for NLR; 2.6% vs. 10.5%, HR: 1.86, 95% CI [1.73, 2.01], P < 0.001 for PLR; and 2.3% vs. 16.3%, HR: 2.37, 95% CI [2.07, 2.72], P < 0.001 for mGPS).
Conclusions: Preoperative CAR, NRL, PLR, and mGPS were associated with postoperative mortality. Our findings may be helpful in predicting mortality after non-cardiac surgery.

Keywords: Biomarkers; General surgery; Inflammation; Mortality; Nutritional status; Patient outcome assessment.

Introduction

The number of major non-cardiac surgeries performed annually is now over 300 million cases, and they are frequently recommended for older patients in more comorbid populations due to advancements in surgical techniques and perioperative care [1]. Postoperative mortality imposes one of the largest mortality cause in developed countries [2], and perioperative care remains challenging because of the additive effects of metabolic burden from surgical stress and the frailty of patients. Therefore, it is difficult for a single biomarker to adequately reflect perioperative risk.

Recently, increasing evidence has indicated that combining various markers of systemic inflammatory response or nutritional condition could better reflect clinical prognosis [3–17]. A number of combinations using inflammation-based and nutritional biomarkers such as C-reactive protein (CRP)-to-albumin ratio (CAR) [10,16,17], neutrophil-to-lymphocyte ratio (NLR) [11], platelet-to-lymphocyte ratio (PLR) [12], and modified Glasgow Prognostic Score (mGPS) [13] have been proposed to reflect poor prognosis at higher levels. The strength of these indicators is that they can be simply calculated using readily available blood laboratory tests and have been widely investigated as reliable prognostic biomarkers. However, previous studies have tended to be conducted dominantly among critical patients or those with cancer, resulting in a paucity of data for the general surgical population. Therefore, this study used a large cohort of consecutive patients undergoing non-cardiac surgery and aimed to evaluate whether CAR, NLR, PLR, and mGPS are associated with postoperative mortality. Our findings may be helpful for clinicians to distinguish an accurate prognosis index and to provide individualized therapy in relevant fields.

Materials and Methods

The Institutional Review Board (IRB) of our institution approved this study and waived the need for written informed consent because we used a de-identified registry (IRB no. 2021-06-078). The study was conducted following the Declaration of Helsinki-2013, and we reported the result in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Data curation & study population

This study analyzed the data from our NoCop (Non-Cardiac Operation, KCT 0006363) registry that contains data of 203,787 consecutive adult patients who underwent non-cardiac surgery in our institution between January 2011 and June 2019. We generated this large, single-center, de-identified cohort by extracting data from the institutional electronic archive system. Our institutional electronic archive system provides an electronic system that allows researchers to retrieve data from electronic medical records in a de-identified form and is known as "Clinical Data Warehouse Darwin-C." This system can extract medical records of more than four million patients with more than 900 million laboratory findings and 200 million prescriptions. It also provides data on mortality outside the institution, updated from the National Population Registry of the Korea National Statistical Office using a unique personal identification number. Based on an extracted preoperative evaluation sheet, investigators who were blinded to mortality collected relevant preoperative variables, including demographic data and underlying diseases. In our institution, the preoperative evaluation sheet is generated one day prior to surgery and contains the most recent laboratory test results obtained within six months prior to surgery. So, we used the most recent results available within six months before surgery for blood laboratory tests of CRP, albumin, and complete blood count (CBC) that were automatically extracted from the electronic medical records system.

Study endpoints & definitions

The primary endpoint was mortality during the one-year follow-up after surgery. The secondary endpoint was mortality during three-year follow-up.

The mGPS was calculated from baseline CRP and albumin as follows: score 0; CRP ≤ 10 mg/L, score 1; CRP > 10 mg/L and albumin ≥ 3.5 g/dl, and score 2; CRP > 10 mg/L and albumin < 3.5 g/dl [13]. The other prognostic indicators were determined using the following formula: (1) NLR = absolute neutrophil count/absolute lymphocyte count; (2) PLR = absolute platelet count/absolute lymphocyte count; (3) CAR = CRP/albumin [18].

Statistical analysis

The categorical variables were presented as numbers with percentages, and continuous variables were expressed as mean ± standard deviation or median with median (Q1, Q3) as appropriate. The categorical variables were compared using the Chi-square test, and continuous variables were compared using the t-test or the Mann-Whitney test. To estimate the optimal cut-off value of CAR, NLR, and PLR associated with one-year mortality, receiver operating characteristic (ROC) curve analysis was performed, and Youden's index was calculated. The cut-off values were determined based on the point on the ROC curve that maximized the sum of sensitivity and specificity, as indicated by Youden's index, with values above this indicating a higher risk of one-year mortality. So, these cut-off values were chosen based on their ability to distinguish between patients with a higher or lower risk of one-year mortality. The preoperative mGPS score was divided into three groups (0, 1, and 2), and 0 was selected as the cut-off value [3,5]. Based on the estimated cut-off value, patients were classified into low and high groups, and their mortalities were compared using the Cox regression analysis. The results were reported as hazard ratio (HR) with 95% CI. To reduce bias and achieve a bal-

ance between the groups, we conducted adjustments with inverse probability weighting (IPW) using the propensity score for all relevant variables [19]. Through this method, weights for patients with higher values were the inverse of the propensity score, and weights for patients with lower values and standardized mean difference less than 10% were considered balance between the groups. In addition, we performed a sensitivity analysis by conducting subgroup analysis for postoperative treatment such as postoperative intensive care treatment, transfusion, and dialysis, as these factors could also affect mortality. Kaplan-Meier curves were generated for mortalities and compared with the log-rank tests. Based on the sample size, the power of our analysis was 0.99 when the HR was greater than 1.1 [20]. All statistical analysis in this study was performed by R 4.2.0 (Vienna, Austria; http://www.R-project.org/). All tests were two-tailed, and a P value less than 0.05 was considered statistically significant.

Results

This study demonstrated the associations between preoperative inflammatory and nutrition-based markers and mortality after non-cardiac surgery. From a total of 203,787 patients in the SMC-NoCop registry, we excluded 101,735 without fully available CRP, albumin, and CBC results six months before surgery. Finally, 102,052 (50.1%) patients were enrolled for analysis. The baseline characteristics of the patients according to one-year mortality are summarized in Table 1. The median durations from blood laboratory tests to surgery were 11.5 (median 1.7, 23.4) days for CAR and 10.3 (median 1.4, 21.3) for complete blood cell counts that were used to estimate NLR and PLR. Of the 102,052 patients, there were 4,240 (4.2%) who exhibited one-year mortality. These patients were older, male dominant, and had a higher prevalence of most comorbidities. They also experienced more emergencies and underwent intermediate to high-risk surgeries. Preoperative median values of CAR, NLR, PLR, and number of patients with mGPS > 0 were higher in patients with one-year mortality.

We generated the ROC curve for each index, and the area under the curve of CAR, NLR, PLR, and mGPS were 0.796, 0.743, 0.670, and 0.708, respectively (Fig. 1). Based on the maximum Youden's index, the optimal cut-off threshold values of CAR, NLR, and PLR were 0.76, 2.78, and 11.70 for one-year mortality, respectively. According to these calculated cut-off values, patients were classified into low and high groups: 76,732 (75.2%) vs. 25,320 (24.5%) for CAR; 77,129 (75.6%) vs. 24,923 (24.4%) for NLR; 82,228 (80.6%) vs. 19,824 (19.4%) for PLR; and 88,740 (87.0%) vs. 13,312 (13.0%) for mGPS (0 vs. 1–2). The baseline characteristics are compared according to these values in Supplementary Tables 1–4. In all types of inflammatory indices, the high groups exhibited higher values and greater incidence of relevant risk factors. The Kaplan-Meier curves displaying survival rates at one-year after surgery according to inflammatory index are shown in Fig. 2. After an adjustment for the IPW technique, high CAR, NLR, PLR, and mGPS groups were significantly associated with increased risk of one-year mortality (1.7% vs. 11.7%, HR: 2.38, 95% CI [2.05, 2.76], P < 0.001 for CAR; 2.2% vs. 10.3%, HR: 1.81, 95% CI [1.62, 2.03], P < 0.001 for NLR; 2.6% vs. 10.5%, HR:

Table 1. Baseline Characteristics according to Mortality during One-year Follow-up

Variable	No mortality (n = 97,812)	Mortality (n = 4,240)	P value
CAR	0.19 (0.08, 0.65)	2.94 (0.51, 12.71)	< 0.001
NLR	1.83 (1.34, 2.66)	3.45 (2.07, 6.50)	< 0.001
PLR	7.48 (5.71, 10.28)	11.41 (6.97, 19.87)	< 0.001
mGPS			< 0.001
0	86676 (88.6)	2064 (48.7)	
1	8482 (8.7)	1053 (24.8)	
2	2654 (2.7)	1123 (26.5)	
CRP (mg/L)	0.8 (0.3, 2.8)	10.9 (2.1, 43.6)	< 0.001
Albumin (g/dl)	4.4 (4.1, 4.6)	3.8 (3.3, 4.2)	< 0.001
Neutrophil (%)	57.9 (50.9, 65.7)	68.8 (58.9, 78.9)	< 0.001
Lymphocyte (%)	31.7 (24.6, 38.3)	19.9 (11.9, 28.6)	< 0.001
Platelet (cells/μl)	235K (196K, 277K)	227K (159K, 294K)	< 0.001
M	48322 (49.4)	2750 (64.9)	< 0.001
Age (yr)	55.8 ± 15.3	62.5 ± 13.1	< 0.001
Body mass index (kg/m^2)	24.3 ± 3.7	22.6 ± 3.5	< 0.001

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Table 1. Continued

Variable	No mortality (n = 97,812)	Mortality (n = 4,240)	P value
ASA physical classification			< 0.001
I	33721 (34.5)	403 (9.5)	
II	55818 (57.1)	2587 (61.0)	
III	7858 (8.0)	997 (23.5)	
IV	398 (0.4)	145 (3.4)	
V	17 (0.0)	108 (2.5)	
Habitual risk factor			
Current alcohol	19666 (20.1)	494 (11.7)	< 0.001
Current smoking	8308 (8.5)	281 (6.6)	< 0.001
Previous disease			
Hypertension	30837 (31.5)	1465 (34.6)	< 0.001
Diabetes	13959 (14.3)	908 (21.4)	< 0.001
Chronic kidney disease	2569 (2.6)	150 (3.5)	< 0.001
Dialysis	725 (0.7)	64 (1.5)	< 0.001
Stroke	2818 (2.9)	225 (5.3)	< 0.001
Coronary artery disease	2738 (2.8)	152 (3.6)	< 0.001
Heart failure	466 (0.5)	47 (1.1)	< 0.001
Arrhythmia	1936 (2.0)	195 (4.6)	< 0.001
Peripheral artery disease	429 (0.4)	23 (0.5)	0.384
Aortic disease	506 (0.5)	43 (1.0)	< 0.001
Valvular heart disease	192 (0.2)	11 (0.3)	< 0.001
Chronic obstructive pulmonary disease	2328 (2.4)	191 (4.5)	< 0.001
Preoperative blood laboratory tests			
Hemoglobin (g/dl)	13.3 ± 1.8	11.7 ± 1.7	< 0.001
Creatinine (mg/dl)	1.0 ± 1.0	1.0 ± 0.9	0.081
Operative variables			
General anesthesia	78621 (80.4)	3793 (89.5)	< 0.001
Emergency operation	7421 (7.6)	1100 (25.9)	< 0.001
Operation duration (min)	134.5 ± 100.6	166.7 ± 143.9	< 0.001
Intraoperative transfusion	4190 (4.3)	740 (17.5)	< 0.001
Intraoperative inotropics infusion	10120 (10.3)	1126 (26.6)	< 0.001
Surgical risk			
Mild	28243 (28.9)	651 (15.4)	< 0.001
Intermediate	64402 (65.8)	2892 (68.2)	0.002
High	5167 (5.3)	697 (16.4)	< 0.001
Surgery types			
Neuroendocrine	747 (0.8)	7 (0.2)	
Lung	8187 (8.4)	679 (16.0)	
Head & neck	12514 (12.8)	847 (20.0)	
Breast	1167 (1.2)	12 (0.3)	
Stomach	1336 (1.4)	128 (3.0)	
Hepatobiliary	6662 (6.8)	542 (12.8)	
Colorectal	12442 (12.7)	610 (14.4)	
Urology	12308 (12.6)	351 (8.3)	
Gynecology	7813 (8.0)	80 (1.9)	
Bone, skin, etc.	34636 (35.4)	984 (23.2)	

Values are presented as median (Q1, Q3), number (%) or mean ± SD. Surgical risk was stratified according to the 2014 European Society of Cardiology/European Society of Anesthesiology guidelines. CAR: CRP-to-albumin ratio, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, mGPS: modified Glasgow Prognostic Score, CRP: C-reactive protein, ASA: American Society of Anesthesiologists.

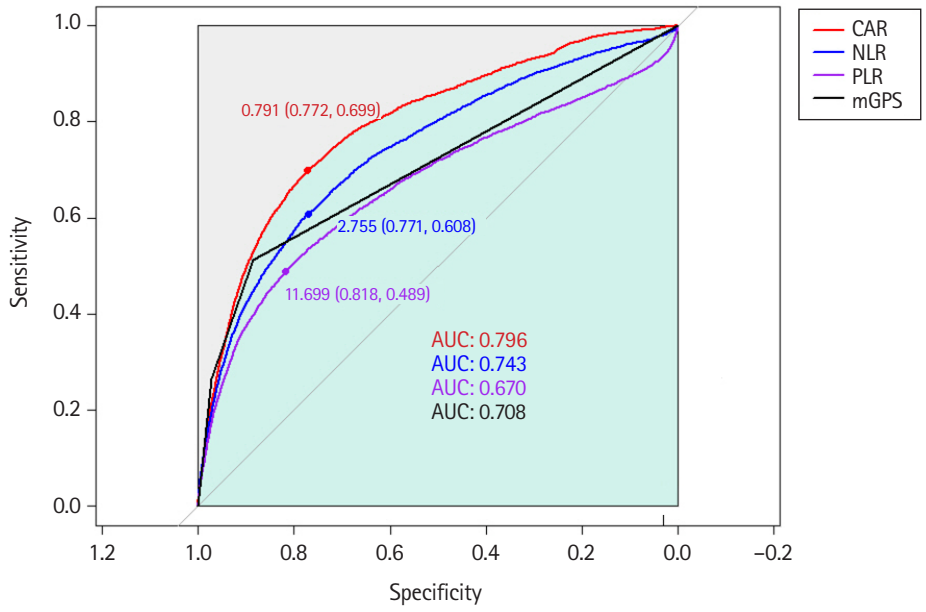

Fig. 1. Receiver-operating curve (ROC) plots for the associations of C-reactive protein-to-albumin ratio (CAR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and modified Glasgow Prognostic Score (mGPS) with one-year mortality and the optimal threshold estimated using Youden's index with 95% CI. AUC: under the curve.

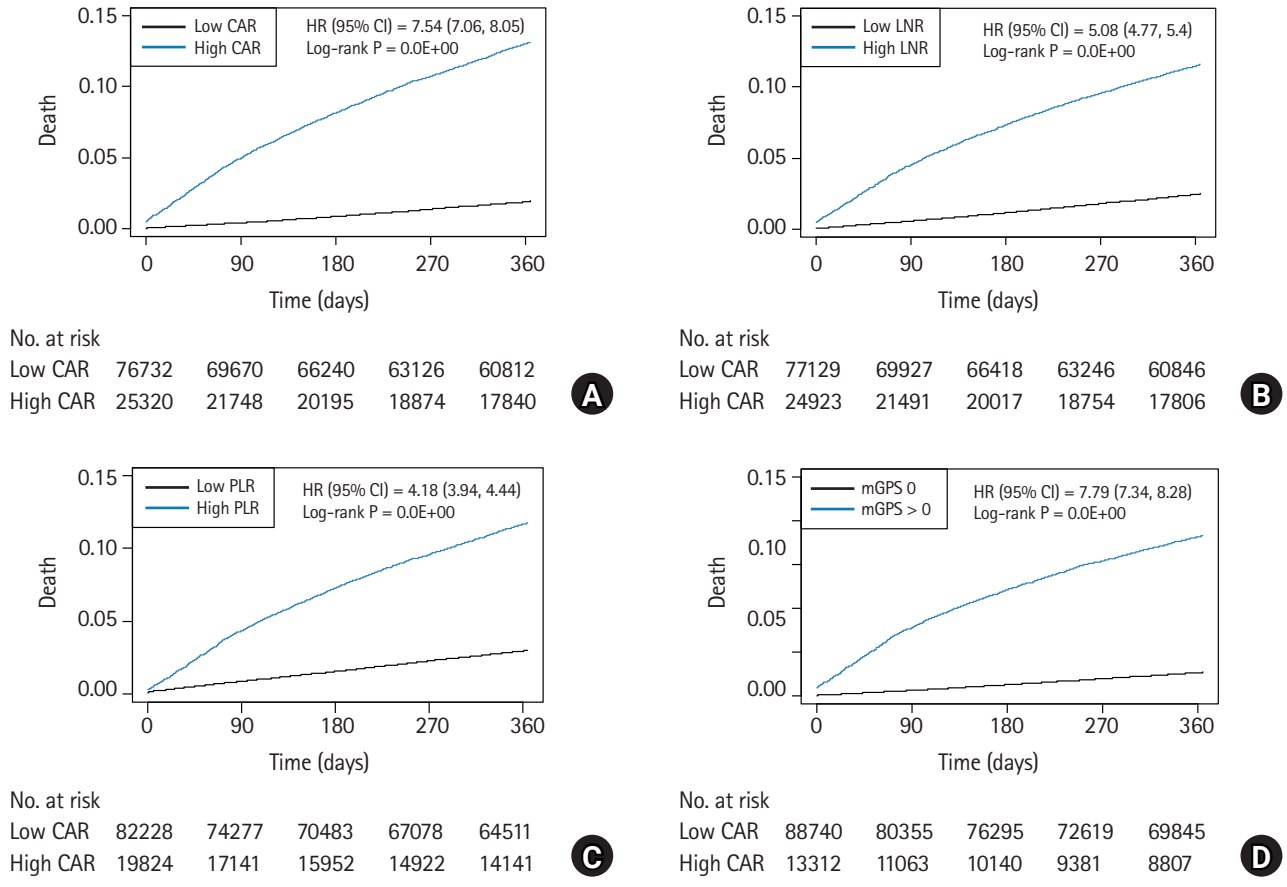

Fig. 2. Kaplan-Meier curves for one-year mortality according to (A) C-reactive protein-to-albumin ratio (CAR) > 0.76, (B) neutrophil-to-lymphocyte ratio (NLR) > 2.78, (C) platelet-to-lymphocyte ratio (PLR), > 11.70, and (D) modified Glasgow Prognostic Score (mGPS) (0/1 or 2). HR: hazard ratio.

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Table 2. Mortality according to Estimated Threshold of CAR > 0.76, NLR > 2.78, PLR > 11.70, and mGPS > 0

Markers	Low group	High group	Unadjusted analysis		IPW analysis	
			HR (95% CI)	P value	HR (95% CI)	P value
CAR > 0.76	N = 76,732	N = 25,320				
One-year mortality	1275 (1.7)	2965 (11.7)	7.54 (7.06, 8.05)	< 0.001	2.38 (2.05, 2.76)	< 0.001
Three-year mortality	3249 (4.2)	4797 (18.9)	4.95 (4.73, 5.17)	< 0.001	2.15 (1.97, 2.34)	< 0.001
NLR > 2.78	N = 77,129	N = 24,923				
One-year mortality	1665 (2.2)	2575 (10.3)	5.08 (4.77, 5.40)	< 0.001	1.81 (1.62, 2.03)	< 0.001
Three-year mortality	3933 (5.1)	4113 (16.3)	3.51 (3.37, 3.68)	< 0.001	1.71 (1.60, 1.84)	< 0.001
PLR > 11.70	N = 82,228	N = 19,824				
One-year mortality	2168 (2.6)	2072 (10.5)	4.18 (3.94, 4.44)	< 0.001	1.86 (1.73, 2.01)	< 0.001
Three-year mortality	4685 (5.7)	3361 (17.0)	3.24 (3.10, 3.39)	< 0.001	1.81 (1.72, 1.92)	< 0.001
mGPS > 0	N = 88,740	N = 13,312				
One-year mortality	2064 (2.3)	2176 (16.3)	7.79 (7.34, 8.28)	< 0.001	2.37 (2.07, 2.72)	< 0.001
Three-year mortality	4824 (5.4)	3222 (24.2)	5.16 (4.94, 5.40)	< 0.001	2.11 (1.92, 2.32)	< 0.001

Values are presented as number (%). CAR: CRP-to-albumin ratio, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, mGPS: modified Glasgow Prognostic Score, IPW: inverse probability weighting, HR: hazard ratio.

1.86; 95% CI [1.73, 2.01], P < 0.001 for PLR; and 2.3% vs. 16.3%, HR: 2.37, 95% CI [2.07, 2.72], P < 0.001 for mGPS) (Table 2). This relationship persisted for three-year mortality (4.2% vs. 18.9%, HR: 2.15, 95% CI [1.97, 2.34], P < 0.001 for CAR; 5.1% vs. 16.3%, HR: 1.71, 95% CI [1.60, 1.84], P < 0.001 for NLR; 5.7% vs. 17.0%, HR: 1.81, 95% CI [1.72, 1.92], P < 0.001 for PLR; and 5.4% vs. 24.2%, HR: 2.11, 95% CI [1.92, 2.32], P < 0.001 for mGPS). In subgroup analysis, we did not observe a significant interaction for the association between mortality and the estimated threshold of each index (Table 3).

Discussion

This study demonstrated an association between preoperative CAR, PLR, NLR, and mGPS and postoperative mortality after non-cardiac surgery. Patients with higher values than the estimated thresholds exhibited an increased risk of mortality after statistical adjustment. These indicators showed a fair ability to predict postoperative one-year mortality, and CAR showed the best predictive performance.

Inflammation and nutritional impairment are associated with increased adverse outcomes in various clinical settings. Although combinations of inflammatory or nutrition-related markers have been widely evaluated to demonstrate this relationship, few studies have investigated the associations in surgical populations. In patients anticipating scheduled surgery, the presence of infection, comorbidities, and malnutrition could induce inflammation and deterioration of nutritional status [21–24]. Therefore, we hypothesized that preoperative inflammation and nutritional state could predict postoperative outcomes in patients undergoing non-cardiac surgery. In this study, we conducted a comprehensive analysis of the previously reported combinations of inflammatory or nutrition-related markers and demonstrated a significant relationship with mortality after non-cardiac surgery during one-year follow-up.

The predictive performance for one-year mortality shown in the ROC curves was higher for CAR compared with NLR and PLR. CAR is a novel and promising biomarker that is calculated as the ratio of serum CRP and albumin levels. CRP is a major indicator of an acute-phase inflammatory response, and hypoalbuminemia indicates malnutrition as well as the severity of inflammation and disease progression [24,25]. In surgical patients, the pre-existing inflammatory condition could exacerbate malnutrition and markedly augment inflammatory response to surgical injuries [26] that could have directly affected mortality. By combining these two indicators, CAR seems to appropriately reflect both inflammatory and nutritional statuses in the preoperative period. This well explains our result that CAR exhibited higher predictive value compared with other biomarkers based only on inflammatory cell count.

The mGPS uses the same laboratory variables as CAR but stratifies patients into a certain number instead of providing a value as a continuous variable. It is also known as one of the most effective biomarkers for predicting prognosis. Numerous studies simultaneously investigated the prognostic values of mGPS and CAR for cancer patients and showed comparable predictive performances [5,7,27]. According to our analysis, CAR demonstrated a slightly better predictive value for postoperative mortality compared to

Table 3. Subgroup Analysis according to Postoperative Treatment on Association between One-year Mortality and the Estimated Threshold of CAR > 0.76, NLR > 2.78, PLR > 11.70, and mGPS > 0

Markers	Low group	High group	HR (95% CI)	P value	P value for interaction
CAR > 0.76					
No intensive care treatment	65586 (77.1)	19440 (22.9)	8.44 (7.76, 9.18)	< 0.001	< 0.001
Intensive care treatment	11146 (65.5)	5880 (34.5)	4.81 (4.33, 5.35)	< 0.001	
No postoperative transfusion	67070 (77.5)	19478 (22.5)	6.52 (6.02, 7.06)	< 0.001	< 0.001
Postoperative transfusion	9662 (62.3)	5842 (37.7)	7.10 (6.29, 8.00)	< 0.001	
No postoperative dialysis	76557 (75.3)	25094 (24.7)	7.56 (7.08, 8.07)	< 0.001	0.081
Postoperative dialysis	175 (43.6)	226 (56.4)	2.95 (1.46, 5.97)	0.003	
NLR > 2.78					
No intensive care treatment	65619 (77.2)	19407 (22.8)	5.29 (4.89, 5.72)	< 0.001	< 0.001
Intensive care treatment	11510 (67.6)	5516 (32.4)	3.81 (3.44, 4.21)	< 0.001	
No postoperative transfusion	67050 (77.5)	19498 (22.5)	4.65 (4.31, 5.03)	< 0.001	< 0.001
Postoperative transfusion	10079 (65.0)	5425 (35.0)	4.36 (3.92, 4.84)	< 0.001	
No postoperative dialysis	77010 (75.8)	24641 (24.2)	5.08 (4.78, 5.41)	< 0.001	0.075
Postoperative dialysis	119 (29.7)	282 (70.3)	1.96 (0.91, 4.22)	0.081	
PLR > 11.70					
No intensive care treatment	69372 (81.6)	15654 (18.4)	4.64 (4.30, 5.01)	< 0.001	0.542
Intensive care treatment	12856 (75.5)	4170 (24.5)	3.00 (2.72, 3.31)	< 0.001	
No postoperative transfusion	70968 (82.0)	15580 (18.0)	4.26 (3.95, 4.60)	< 0.001	< 0.001
Postoperative transfusion	11260 (72.6)	4244 (27.4)	3.09 (2.08, 3.41)	< 0.001	
No postoperative dialysis	81977 (80.6)	19674 (19.4)	4.20 (3.95, 4.46)	< 0.001	0.664
Postoperative dialysis	251 (62.6)	150 (37.4)	1.78 (0.99, 3.21)	0.062	
mGPS > 0					
No intensive care treatment	75229 (88.5)	9797 (11.5)	9.02 (8.35, 9.74)	< 0.001	< 0.001
Intensive care treatment	13511 (79.4)	3515 (20.6)	4.59 (4.16, 5.06)	< 0.001	
No postoperative transfusion	76918 (88.9)	9630 (11.1)	6.90 (6.39, 7.45)	< 0.001	< 0.001
Postoperative transfusion	11822 (76.3)	3682 (23.7)	6.33 (5.73, 7.01)	< 0.001	
No postoperative dialysis	88482 (87.0)	13169 (13.0)	7.82 (7.36, 8.31)	< 0.001	0.054
Postoperative dialysis	258 (64.3)	143 (35.7)	3.23 (1.76, 5.92)	0.002	

Values are presented as nunber (%). CAR: CRP-to-albumin ratio, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, mGPS: modified Glasgow Prognostic Score, HR: hazard ratio.

mGPS. This seems to be owing to the difference in our population that the majority (87%) of patients had mGPS of 0, with only 13% of patients having mGPS values of 1 or 2. This low prevalence of mGPS of 1 and 2 that is associated with poor prognosis could have reduced the discrimination power of mGPS in our cohort. On the other hand, considering that CAR can further classify patients with mGPS of 0 into good and poor prognosis groups, CAR may be a more sensitive marker for predicting postoperative mortality in relatively healthier populations compared to cancer patients. Further research is required for a better understanding of the role of inflammation and nutrition-based markers in relation to mortality after non-cardiac surgery.

The following limitations should be acknowledged when interpreting our results. This is a single-center retrospective study, and residual confounding factors may have affected our results despite proper statistical adjustments. Second, preoperative CRP, albumin, and blood cell counts were selectively obtained. This may have caused a selection bias. Third, the best cut-off values of the markers varied in published reports, potentially weakening the clinical application and generalization of our results. The optional cut-off in non-cardiac surgery has yet to be universally established and must be verified in multicenter and larger cohort studies. Last, our study could not determine whether an improvement in inflammatory and nutritional markers is helpful for postoperative mortality. Future studies are necessary to propose an adequate intervention for patients with high inflammatory and nutritional markers.

Despite these limitations, our study demonstrated associations

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between preoperative inflammation and nutrition-based markers and postoperative mortality after non-cardiac surgery.

Our study suggests that these indicators could be considered in predicting the long-term prognosis of non-cardiac surgery, and CAR may be the most useful marker. These results may lead to future studies on therapeutic interventions for those with elevated inflammation and nutrition-related biomarkers.

In conclusion, preoperative CAR, NRL, PLR, and mGPS were associated with postoperative mortality after non-cardiac surgery. These inflammation and nutrition-based markers may be helpful in predicting postoperative mortality after non-cardiac surgery. Further extensive studies are warranted to confirm our results.

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None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Ah Ran Oh (Conceptualization; Data curation; Formal analysis; Validation; Writing – original draft)
Jungchan Park (Conceptualization; Formal analysis; Supervision; Writing – original draft; Writing – review & editing)
Jong-Hwan Lee (Supervision; Writing – review & editing)
Kwangmo Yang (Software; Supervision; Validation)
Joonghyun Ahn (Formal analysis)
Seung-Hwa Lee (Supervision; Validation; Writing – review & editing)
Sangmin Maria Lee (Supervision; Writing – review & editing)

Supplementary Materials

Supplementary Table 1. Baseline characteristics according to estimated threshold of C-reactive protein/albumin ratio > 0.76.
Supplementary Table 2. Baseline characteristics according to estimated threshold of neutrophil/lymphocyte ratio > 2.78
Supplementary Table 3. Baseline characteristics according to estimated threshold of platelet/lymphocyte ratio > 11.70
Supplementary Table 4. Baseline characteristics according to estimated threshold of modified Glasgow prognostic score > 0

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Does intravenous patient-controlled analgesia or continuous block prevent rebound pain following infraclavicular brachial plexus block after distal radius fracture fixation? A prospective randomized controlled trial

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Background: The purpose of this study was to investigate the role of opioid-based intravenous patient-controlled analgesia (IV PCA) or continuous brachial plexus block (BPB) in controlling rebound pain after distal radius fracture (DRF) fixation under BPB as well as total opioid consumption.

Methods: A total of 66 patients undergoing surgical treatment for a displaced DRF with volar plate fixation were randomized to receive a single infraclavicular BPB (BPB only group) (n = 22), a single infraclavicular BPB with IV PCA (IV PCA group) (n = 22), or a single infraclavicular BPB with continuous infraclavicular BPB (continuous block group) (n = 22). The visual analog scale (VAS) for pain and the amount of pain medication were recorded at 4, 6, 9, 12, 24, and 48 h and two weeks postoperatively.

Results: At postoperative 9 h, the pain VAS score was significantly higher in the BPB only group (median: 2; Q1, Q3 [1, 3]) than in the IV PCA (0 [0, 1.8], P = 0.006) and continuous block groups (0 [0, 0.5], P = 0.009). At postoperative 12 h, the pain VAS score was significantly higher in the BPB only group (3 [3, 4]) than in the continuous block group (0.5 [0, 3], P = 0.004). The total opioid equivalent consumption (OEC) was significantly higher in the IV PCA group (350.3 [282.1, 461.3]) than in the BPB only group (37.5 [22.5, 75], P < 0.001) and continuous block group (30 [15, 75], P < 0.001); however, OEC was not significantly different between the BPB only group and the continuous block group (P = 0.595).

Conclusions: Although continuous infraclavicular BPB did not reduce total opioid consumption compared to BPB only, this method is effective for controlling rebound pain at postoperative 9 and 12 h following DRF fixation under BPB.

Keywords: Brachial plexus blockade; Breakthrough pain; Catheters; Distal radius fracture; Patient-controlled analgesia; Regional anesthesia.

Introduction

Distal radius fractures (DRFs) account for up to 15% of all extremity fractures [1]. Open reduction and internal fixation using volar locking anatomical plate and screws is the most frequently performed surgical procedure [2,3]. Poor pain control in the acute postoperative period is associated with patient dissatisfaction after operation [4].

Operative treatments of extremity fractures under regional anesthesia have several ad-

vantages as compared with general anesthesia, including muscle relaxation and analgesia in the acute postoperative period without the requirement of tracheal intubation that is relevant to patients with underlying lung diseases. Some studies reported that it could prevent postoperative nausea and vomiting and shorten the post-anesthesia care unit (PACU) stay duration [4–6]. In the operative treatment of DRFs, regional anesthesia is better than general anesthesia in reducing postoperative pain and pain medication use [7,8].

Despite the advantages of regional anesthesia, patient dissatisfaction may be attributed to severe pain after the regional anesthesia wears off that is known as "rebound pain"[9]. Rebound pain typically occurs in the 8 to 24 h postoperative period and is often treated with preemptive oral pain medication [10,11]. However, as the timing and intensity of rebound pain are different among individuals, oral medication may not control the pain properly or may cause opioid-related complications due to overuse [4]. Intravenous patient-controlled analgesia (IV PCA) and continuous regional block with an infusion pump would be alternative methods for controlling rebound pain; however, limited studies have been conducted on the control of rebound pain after regional block for DRF fixation.

The purpose of the current randomized controlled trial (RCT) was to investigate the role of IV PCA or continuous brachial plexus block (BPB) in controlling rebound pain after DRF fixation under BPB as well as total opioid consumption.

Materials and Methods

Patients

We performed a randomized controlled study at a single center between December 2018 and April 2019. The study was approved by our Institutional Review Board (Approval number: AMC-2018-1335), registered at the Clinical Research Institution Service (CRIS; Registration number: KCT0003404) and adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. This study was also conducted in accordance with the ethical principles of the Helsinki Declaration 2013. All patients who underwent treatment for a displaced DRF with volar plate fixation (fracture type A, B, or C according to the AO Foundation/Orthopaedic Trauma Association classification system, as examined on radiographs) were assessed for eligibility. The inclusion criteria were age of 18–79 years and the occurrence of DRF within two weeks prior to surgery. The exclusion criteria included a concomitant ulnar fracture proximal to the base of the styloid process; a complex distal radial fracture requiring additional fixation or bone graft; previous ipsilateral wrist or hand dysfunction; previous pain disorder; concomitant nerve, tendon, or skin injury in the fractured wrist; concomitant injury at other sites requiring additional surgery and/or pain medication; ongoing drug or alcohol abuse; severe psychiatric disorder; or systemic inflammatory diseases. Patients who met all the inclusion and exclusion criteria were informed about the study and offered to participate in the study by an orthopedic surgeon. After written consent was obtained, the patients were randomized to receive a single infraclavicular BPB (BPB only group), a single infraclavicular BPB with opioid-based IV PCA (IV PCA group), or a single infraclavicular BPB with continuous infraclavicular BPB (continuous block group) through block randomization (n = 6) using sequentially numbered closed opaque envelopes (Fig. 1).

Interventions

All anesthetic and surgical interventions were performed with standardized protocols. All peripheral nerve block procedures were performed under ultrasonography guidance (Logiq P9; GE Healthcare, USA) by two anesthesiologists with more than five years of experience with peripheral nerve block. After the confirmation of the posterior cord with electrical stimulation, 0.4 to 0.6 ml/kg of the prepared 0.375% ropivacaine, consisting of a mixture of 20 ml 0.75% ropivacaine (Kabiropivacaine; Fresenius Kabi, Norway) and 20 ml normal saline, was administered to all the patients. In the continuous block group, echogenic catheter-over-needle (E-Cath PLUS; PAJUNK, Germany) was used. After the single-block procedure, the needle was removed, and the tip of the catheter remained between the axillary artery and the posterior cord. The catheter was secured to the skin with adhesive tapes when it was properly positioned. The sensory and motor blockades of the patients were evaluated 30 min after the BPB procedure. After confirmation of a successful block, a dose of 1 μg/kg intravenous dexmedetomidine was loaded over 10–15 min, followed by a continuous infusion of 0.5–1.0 μg/kg/h until the end of the operation.

For the IV PCA group, the analgesic was prepared with a mixture of fentanyl citrate (Hana Pharmacy, Korea) and normal saline. The total volume was set to 100 ml; however, the fentanyl citrate dose was determined based on each patient's body weight as follows: < 50 kg, 1000 μg; 50–70 kg, 1200 μg; > 70 kg, 1500 μg. The PCA pump (AutoMed 3200, Ace Medical, Korea) was set for a basal rate of 1 ml/h, a bolus dose of 1 ml, and a locking time of 15 min. For the continuous block group, 250 ml 0.15% ropivacaine, consisting of a mixture of 50 ml 0.75% ropivacaine and 200 ml normal saline, was administered as follows: a basal rate of 5

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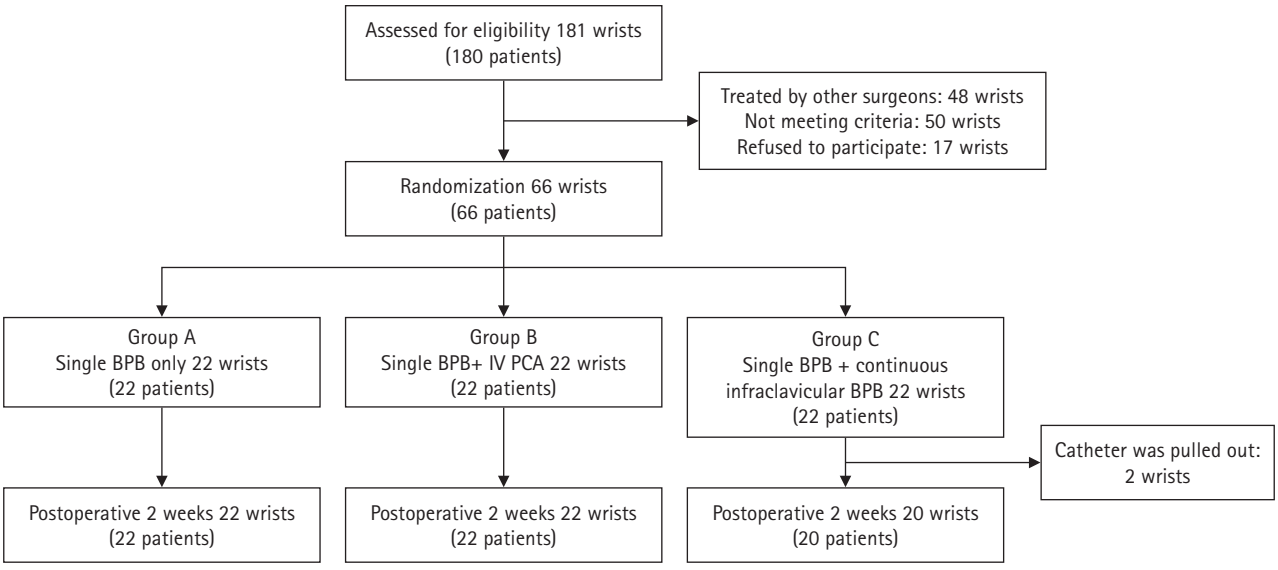

Fig. 1. Flowchart of patient enrollment. BPB: brachial plexus block, IV PCA: intravenous patient-controlled analgesia.

ml/h, a bolus dose of 5 ml, and lockout time of 30 min. The infusion pump was started just before the end of the operation in both groups.

The patients underwent surgery with a volar Henry approach to the distal part of the radius, followed by open reduction and internal fixation with a single volar locking plate (Synthes, Switzerland). All operations were performed by a fellowship-trained orthopedic surgeon. Until two weeks postoperatively, a volar short arm splint was applied.

Postoperatively, the patients were monitored in the PACU for 1–2 h and transferred to the general ward. The patients were instructed to call a nurse for pain medication (1–2 pills of 5 mg of oxycodone hydrochloride [HCL]) every 4–6 h as needed. The pain level was measured by an on-duty nurse with a visual analog scale (VAS; 0 to 10) at 4, 6, 9, 12, 24, and 48 h after surgery. When the timing of pain measurement and medication requirement were similar, pain was measured just before taking medication. IV PCA or infusion pump for continuous BPB was discontinued at 48 h after surgery. If the pump was empty before 48 h, it was discontinued before 48 h. In addition, when hand motor paralysis persisted over 24 h in the continuous block group, the catheter was removed before 48 h to prevent hand stiffness. The patients were discharged on the third day after the operation with 30 pills of 5 mg oxycodone HCL and were instructed to take 1–2 pills every 4–6 h as needed. They were followed up at two weeks after operation for stitches out with an assessment of the pain level and the amount of medication taken.

Methods of assessment

The primary outcome was pain as measured with a VAS at 12 h after operation. The secondary outcome was the total opioid equivalent consumption (OEC) during the two weeks after operation. The VAS score for pain and the amount of pain medication were recorded at 4, 6, 9, 12, 24, and 48 h and two weeks after the operation. The total amount of infused IV PCA or continuous BPB for 48 h after operation and total opioid consumption for two weeks after operation were assessed. All opioid analgesics were converted to opioid equivalents (milligrams of oral morphine). Any postoperative analgesia-related complications were evaluated.

Statistical analysis

To determine the statistical power, the VAS score for pain at 12 h after surgery was used as the primary outcome variable. In a pilot study of 15 patients (five patients in each group), the mean VAS score for pain was 5.2 ± 2.3 in the BPB only group, 3.2 ± 1.1 in the BPB with IV PCA group, and 4.0 ± 2.2 in the continuous block group at 12 h after operation. On the basis of these results, a power analysis revealed that a sample size of 20 patients per group would provide 80% statistical power to detect this effect size between the groups (alpha = 0.05, beta = 0.20) with analysis of variance. To account for a possible follow-up loss of 10%, we aimed to enroll 22 patients in each group (a total sample size of 66 patients).

The characteristics of the patients, including age and body mass index, VAS score for pain and oral medication at each time point, and total opioid consumption, were determined using the Krus-

kal-Wallis test. The Mann-Whitney *U* test was used for the post hoc analysis of between-group comparisons to allow for the number of comparisons performed (three comparisons for each variable). The sex ratio, American Society of Anesthesiologists classification, and fracture type distribution of the patients were compared using the Fisher's exact test.

Results

Patient enrollment

A total of 181 wrists (180 patients) were assessed for eligibility during the study period; 66 wrists (66 patients) were included in the study and randomized to the BPB only (22 wrists), IV PCA (22 wrists), or continuous block group (22 wrists). The baseline characteristics are presented in Table 1. Among the three groups, the patients in the continuous block group were significantly younger; however, this was not statistically significant in the post hoc analysis of the between-group comparisons.

Two patients in the continuous block group were excluded because the infusion pump did not function properly due to catheter migration within 12 h after operation. One patient in the BPB only group required additional intravenous opioid analgesia after oral medication and two patients in the BPB only group and another two patients in the continuous block group required additional oral oxycodone HCL administration after taking 10 mg of oral oxycodone HCL between 9 and 12 h after operation. These five patients were included in the analysis. Finally, 64 patients completed the follow-up until two weeks postoperatively.

Postoperative pain

At 9 h after operation, the VAS score for pain was significantly higher in the BPB only group (median: 2; Q1, Q3 [1, 3]) than in the IV PCA (0 [0, 1.8], P = 0.006) and continuous block groups (0 [0, 0.5], P = 0.009). At 12 h after operation, the VAS score for pain was significantly higher in the BPB-only group (3 [3, 4]) than in the continuous block group (0.5 [0, 3], P = 0.004). The median pain scores at other time points did not differ significantly among the three groups (Fig. 2 and Supplementary Table 1).

Postoperative OEC

From 9 to 12 h after operation, the OEC was significantly higher in the BPB only group (7.5 [7.5, 13.1]) than in the IV PCA (0 [0, 5.6], P = 0.001) and continuous block groups (0 [0, 1.9], P = 0.013) (Fig. 3). From 48 h to two weeks after operation, the OEC was significantly higher in the IV PCA group (48.8 [16.9, 103.1]) than in the BPB only (0 [0, 28.1], P = 0.003) and continuous block groups (11.3 [0, 39.4], P = 0.010). The total OEC including IV PCA during two weeks after operation was significantly higher in the IV PCA group (350.3 [282.1, 461.3]) than in the BPB only (37.5 [22.5, 75], P < 0.001) and continuous block groups (30 [15, 75], P < 0.001). The total OEC was not significantly different between the BPB only and the continuous block groups (P = 0.595, Supplementary Table 2).

Complications

Two patients in the IV PCA group (9.1% of 22 patients) experienced nausea and vomiting from 12 to 24 h after the operation and IV PCA was stopped for a few hours after taking an anti-emetic medication. One patient (5.0% of 20 patients) in the continuous block group had constipation, and a laxative was prescribed. Seven patients in the continuous block group (35.0% of 20 patients) had motor paralysis persisting over 24 h after opera-

Table 1. Baseline Information of the Patients Randomized to the BPB Only, IV PCA, and Continuous Block Groups

Baseline information	All (n = 66)	BPB only group (n = 22)	IV PCA group (n = 22)	Continuous block group (n = 22)	P value
Age (yr)	63 (57, 70)	62 (57, 66.5)	67 (62, 73.8)	59 (46.8, 63.8)	0.030*
BMI (kg/m^2)	23.9 (22.0, 25.9)	23.8 (21.8, 25.9)	23.6 (21.9, 25.5)	24.6 (22.1, 26.4)	0.636
Sex (F)	52 (78.8)	15 (68.2)	19 (86.4)	18 (81.8)	0.414
Time between injury and operation (d)	5 (3, 7)	5 (4, 6.8)	6 (2, 10.3)	5 (3.3, 6)	0.792
ASA classification (1/2/3)†	12/49/5	6/14/2	1/19/2	5/16/1	0.257
Fracture type (A/B/C)‡	3/11/52	1/5/16	1/3/18	1/3/18	0.946

Values are presented as median (Q1, Q3), number (%) or number of patients. BPB: brachial plexus block, IV PCA: intravenous patient-controlled analgesia, BMI: body mass index, ASA: American Society of Anesthesiologists. *P value < 0.05 is considered significant. †Classification of the patients' health and comorbidity levels according to the ASA system. ‡Fracture classification according to the AO Foundation/Orthopedic Trauma Association system.

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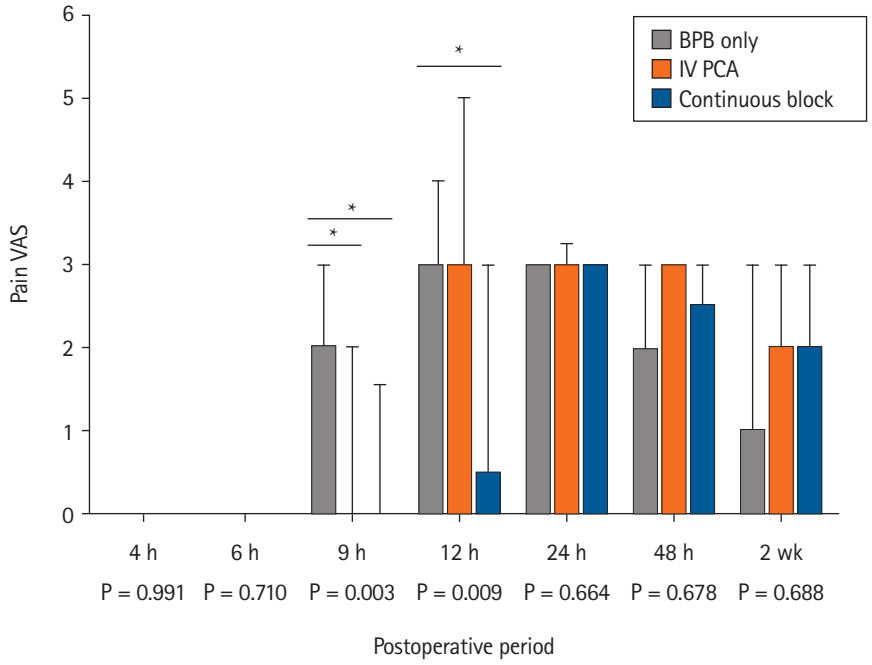

Fig. 2. Box plot showing the median VAS score for pain in the two-week postoperative period for 66 patients randomized to the following groups: BPB (BPB only group), single infraclavicular BPB with IV PCA (IV PCA group), and single infraclavicular BPB with continuous infraclavicular BPB (continuous block group). BPB: brachial plexus block, IV PCA: intravenous patient-controlled analgesia, VAS: visual analog scale. The horizontal bar indicates the median, and the upper bound indicates the third quartile. *P < 0.017.

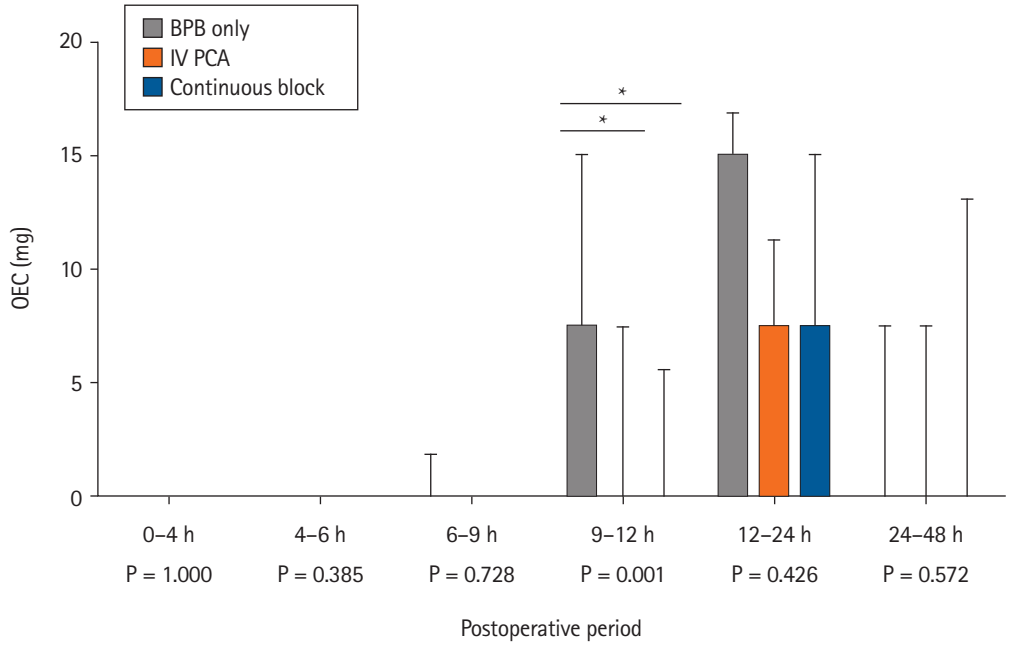

Fig. 3. Box plot showing the oral OEC in the 48 h postoperative period for 66 patients randomized to the following groups: BPB (BPB only group), single infraclavicular BPB with intravenous patient-controlled analgesia IV PCA (IV PCA group), and single infraclavicular BPB with continuous infraclavicular BPB (continuous block group). BPB: brachial plexus block, IV PCA: intravenous patient-controlled analgesia, OEC: opioid equivalent consumption. The horizontal bar indicates the median, and the upper bound indicates the third quartile. *P < 0.017.

tion, and the catheter was removed before 48 h after operation. They were encouraged to perform active-assisted range-of-motion exercise for all fingers and did not have hand stiffness at two weeks after operation.

Discussion

Rebound pain could be controlled by timed pain medication in the wear-off period of regional anesthesia; however, correctly timed pain medication at an appropriate level is difficult for several reasons. First, the timing of rebound pain varies even with the same type of operation, for example, 12–24 h for extremity fracture fixation [9,12], and 1–2 days for shoulder arthroscopy [13]. In addition, depending on the operation time and patient condition, the duration of regional block would be changed [12]. Second, patients are often reluctant to take pain medications especially opioids when they are not yet in pain [12]. Third, the extent of rebound pain varies among patients who underwent the same procedure. After DRF fixation under BPB, one study reported a median VAS score for pain of 3 with an IQR of 3, but another study described a mean VAS score for pain of 5.5 with a SD of 2.4 at the same time point (24 h after operation) [7,8]. Therefore, the amount of pain medication required is not predictable, and inadequate prediction could lead to the abuse or overdose of pain medication without the proper pain management. This RCT revealed that instead of oral pain medication, continuous infraclavicular BPB reduced the intensity and duration of rebound pain in the wear-off period of BPB and had a total OEC similar to that in BPB only.

The role of continuous block for the control of rebound pain after regional block was demonstrated in various extremity surgeries. Continuous interscalene block showed better pain control and a lesser requirement of pain medication than single block in shoulder surgery in several RCTs [14–16]. After anterior cruciate ligament reconstruction, continuous femoral nerve block showed longer pain-free time and lesser rebound pain than single block [17]. In an RCT for patients with ankle fracture fixation, continuous popliteal sciatic nerve block showed lesser rebound pain and opioid consumption than single block [12]. However, in an RCT for patients with DRF fixation, postoperative pain was not significantly different between the continuous infraclavicular block and the single block [9]. Several limitations existed in the previous RCT to consider it as a final report about the effect of continuous block in patients with DRF fixation. Randomization between the continuous and single blocks was partial due to logistical barriers, pain medication in the PACU was not recorded, and pain scores were recorded by the patients themselves that means the pain score at the current time point could be influenced by the numerical value at previous time points.

Catheter migration could occur both in the lower and upper extremities and is an obstacle for the clinical use of continuous block. After continuous popliteal sciatic nerve block for pain control after ankle fracture surgery, 5 of 23 patients (21.7%) experienced an unintentional dislodgement of their catheter during the early postoperative period [12]. After continuous interscalene block for pain control after rotator cuff repair surgery, 1 of 22 patients (4.5%) experienced an accidental removal of their catheter [18]. In our study, 2 of 22 patients (9.1%) revealed catheter migration at an unknown timing. The cause of catheter migration is unclear [19], but temporary motor paralysis of the involved extremities that could not be patient-controlled could increase the risk of unintentional catheter migration. Therefore, clinicians should explain the possibility of catheter migration to the patients and advise against vigorous movement of their extremities during the acute postoperative period.

Delayed sensory and motor recovery after continuous block is an inevitable complication. Several studies informed the risk of fall in patients with continuous femoral nerve block and pressure injury of insensate extremities [19]. Concentration, volume, and infusion rate of continuous block could influence the preservation of more motor function and proprioception, but the correct relationship is unclear and different depending on the anatomic locations [20]. We utilized continuous infraclavicular BPB with relatively low concentration—0.15% ropivacaine—to minimize the risk of prolonged insensation and paralysis. However, a considerable number of patients had motor paralysis persisting over 24 h after operation. Patients could experience anxiety about their paralyzed extremity, but explanation in advance and reassurance could relieve this anxiety. In addition, prompt catheter removal reversed the paralysis, and acute postoperative pain was not an issue after 24 h. Hand and finger stiffness could occur after paralysis, but it could be controlled by active-assisted range-of-motion exercise for all fingers and no sequelae remained in our patients.

Prescription opioid abuse is an increasing problem and has been associated with an increase in opioid overdose-related deaths [21,22]. Orthopedic surgeons represent the third largest group of opioid prescribers in the United States [23], and upper extremity surgeons tend to overprescribe opioids for postoperative pain control [24]. Therefore, development of a protocol to control pain after DRF fixation, which is a common procedure, with minimal OEC is important. In this study, the IV PCA group showed significantly lower pain VAS scores at postoperative 9 h with significantly lower OEC between postoperative 9 and 12 h than the BPB only group. In addition, the complication rate was lower than that of the continuous block group. However, compared with other

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groups, more oral opioids were required after the acute postoperative period between 48 h and two weeks. This phenomenon may be attributed to prior continuous opioid infusion during the acute postoperative period (opioid tolerance) [25].

This study has several limitations. First, all operations were performed after hospitalization that may not reflect the reality of many institutes performing DRF fixation ambulatory surgery. However, we think that the outcome variables, including the pain level at each time point, timing and amount of oral medication, and infused dosage of IV PCA or continuous block, could be assessed more accurately in the hospitalization setting. Second, postoperative pain levels determined on the basis of VAS scores are subjective and might be influenced by psychological factors and personal experience. In addition, pain level was evaluated by different on-duty nurses and not by a single evaluator in this study. Third, intra-venous dexmedetomidine that was used in this study for patient sedation could influence the acute postoperative pain and the amount of required pain medication. Fourth, all the study participants, including the orthopedic surgeon, anesthesiologists, duty nurses, and patients, were not blinded to the type of additional pain control after BPB. Finally, we did not use any adjuvants such as dexamethasone. Several studies revealed that the use of dexamethasone could prolong the duration of the nerve block and reduce rebound pain [26–28]. A well-designed further study is required to compare the effects of catheterization and dexamethasone on rebound pain and cost-effectiveness.

In conclusion, our data suggest that continuous infraclavicular BPB reduced the intensity and duration of rebound pain in the wear-off period of BPB. In addition, the total OEC was similar to that in the BPB only group. Although continuous infraclavicular BPB did not reduce total opioid consumption compared to BPB only, this method is effective for controlling rebound pain at postoperative 9 and 12 h following DRF fixation under BPB.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Author Contributions

Jong-hyuk Lee (Conceptualization; Investigation; Methodology; Project administration; Resources; Writing – review & editing)
Ha-jung Kim (Conceptualization; Investigation; Methodology; Project administration; Resources; Writing – review & editing)
Jae Kwang Kim (Methodology; Project administration; Resources; Writing – review & editing)
Sungjoo Cheon (Investigation; Methodology; Resources; Validation)
Young Ho Shin (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – original draft; Writing – review & editing)

Supplementary Materials

Supplementary Table 1. Visual analogue scale scores for postoperative pain.
Supplementary Table 2. Median opioid equivalent consumption (OEC) in the 2-week postoperative period.

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Quality of recovery in hospital and disability-free survival at three months after major abdominal surgery

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Background: The Quality of Recovery-15 (QoR-15) and 12-item World Health Organization Disability Assessment Schedule 2.0 scales are post-surgery patient-reported outcome measures. We aimed to evaluate the association between immediate in-hospital postoperative recovery and mid-term disability-free survival (DFS) after discharge.

Methods: We conducted a prospective observational study at a university hospital and enrolled 260 patients aged ≥ 65 years with cancer who were undergoing elective major abdominal surgery. The association between poor postoperative recovery, defined as a QoR-15 score < 90 on postoperative day (POD) 2, and the DFS three months later was assessed using Fisher's exact test. The odds ratio of poor recovery on POD 2 to DFS was calculated using multiple logistic regression analysis adjusted for prominent factors (age, preoperative frailty, preoperative DFS, surgical duration, and intraoperative blood loss volume).

Results: A total of 230 patients completed the 3-month follow-up. On POD 2, 27.3% of the patients (63/230) had poor recovery. A greater number of patients without poor recovery on POD 2 had DFS at three months after surgery (79.6%) than those with poor recovery (65.1%) (P = 0.026). The adjusted odds ratio of poor recovery on POD 2 to DFS at three months was 0.481 (95% CI [0.233, 0.994]).

Conclusions: Patients with poor recovery on POD 2 were less likely to have DFS three months after abdominal surgery. These findings may allow for early and effective interventions to be initiated based on each patient's condition after abdominal surgery.

Keywords: Aged; General surgery; Neoplasms; Operative surgical procedures; Patient outcome assessment; Postoperative complications.

Introduction

Although traditional postsurgical outcomes, such as postoperative complications and length of hospital stay, remain important, advances in surgical and anesthetic techniques have improved these outcomes to the degree that patient-reported outcome measures arising directly from the patient have gained more attention [1–3].

Quality of recovery is a subjective measurement that covers the physical (pain, nausea, and vomiting), mental (anxiety and depression), and social (return to work and support from medical staff) domains. Although several measures of immediate postoperative recovery have been developed since 2000, the Quality of Recovery-15 (QoR-15) has become the most widely reported measure of recovery in hospitals following surgery [4–6]. Furthermore, disability-free survival (DFS), assessed using the 12-item World Health Organization Disability Assessment Schedule (WHODAS) 2.0, has played an important role

as a mid-term patient-reported outcome measurement for surgical interventions [3,5–8]. Although the influence of anesthetic, surgical, and patient factors on postoperative recovery and their clinical and prognostic importance have previously been investigated [6,9,10], limited research on the association between immediate postoperative recovery in hospital and mid-term DFS after discharge currently exists.

Based on the hypothesis that poor immediate postoperative recovery decreases DFS at three months after abdominal cancer surgery, we aimed to evaluate the following: (1) the association between poor postoperative recovery and DFS, (2) the odds ratio (OR) of poor recovery to DFS, (3) the QoR-15 scores after surgery for patients with and without poor recovery on postoperative day (POD) 2, (4) the effects of poor recovery on postoperative complications, postoperative length of hospital stay, and the postoperative 12-item WHODAS 2.0 scores, and (5) differences in the mean value for each item of the QoR-15 on POD 2 between patients with and without DFS at three months after surgery.

Materials and Methods

Ethical approval

This prospective observational study was approved by the Institutional Review Board at Nara Medical University (Approval number: 2975; April 28, 2021), and written informed consent was obtained from all included patients before enrollment. This study was registered in the University Hospital Medical Information Network (UMIN000044062) and conducted in accordance with the Declaration of Helsinki, 2013.

Inclusion and exclusion criteria

A total of 260 patients aged ≥ 65 years undergoing elective major abdominal surgery (general, urologic, and gynecologic surgery) with a cancer diagnosis associated with a reduced likelihood of DFS were included. Patients were excluded if they had dementia, psychiatric disease requiring treatment, or poor comprehension of Japanese; were undergoing emergent or palliative surgery; or had a planned postoperative hospital stay < 3 days. The research staff recruited patients before surgery at the preoperative anesthesia clinic of our hospital between June 1, 2021 and April 6, 2022.

Data collection

Before surgery, each patient's age, sex, height, weight, American Society of Anesthesiologists physical status score, comorbidities, respiratory function, medication (β-blockers, steroids, and statins), laboratory data (serum albumin and creatinine levels), frailty, handgrip strength, and nutritional status were routinely assessed. Handgrip strength of the dominant hand was measured three times using a digital Jamar hand dynamometer (MG-4800 MORITOH, Japan), and the maximum value was recorded. Preoperative frailty was assessed using the Fried Frailty Phenotype Questionnaire, which includes five domains (fatigue, resistance, ambulation, inactivity, and weight loss). The total score ranges from 0 to 5 points, and frailty is defined as follows: non-frail (robust) = 0 or 1 point; pre-frail = 2 points; and frail = 3–5 points [11]. Nutritional status was assessed using the Mini Nutritional Assessment-Short Form, with a total score ranging from 0 to 14 points. We also collected intraoperative data on the anesthetic agents used (inhalation and intravenous agents), surgical field (general, urologic, and gynecologic), postoperative analgesia (none, patient-controlled epidural analgesia, and intravenous patient-controlled analgesia), surgical duration, and blood loss volume. Postoperative chemotherapy and radiotherapy were assessed as postoperative covariates.

Postoperative quality of recovery

The QoR-15, which was developed to rapidly evaluate the quality of recovery after surgery and anesthesia in clinical settings, was translated into Japanese in 2021 [12,13]. This assessment tool consists of 15 items, including breathing, rest, well-being, pain, nausea, and mental health, with a total score ranging from 0 to 150 points [12]. According to the QoR-15 score, the quality of recovery after surgery is classified as excellent (QoR-15 > 135), good (122 ≤ QoR-15 ≤ 135), moderate (90 ≤ QoR-15 ≤ 121), and poor (QoR-15 < 90) [10,14]. In this study, the QoR-15 was assessed four times: on the day before surgery and on PODs 2, 4, and 7. In the case of discharge within 4 days of surgery, a telephone assessment was conducted to complete the questionnaire on PODs 4 and 7. We determined POD 2 as the first evaluation day after surgery because the dropout rate on POD 1 had been high in our previous study [13].

Disability-free survival

The 12-item WHODAS 2.0, developed to measure disability, has a total score ranging from 0 to 48 points [15]. In clinical settings, this total score is converted to a percentage (0% = no disability and 100% = complete disability) and for this study, DFS was defined as survival with a WHODAS score < 16% [16]. In-

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dividuals who died after surgery were assigned the maximum WHODAS score of 100%. In this study, the 12-item WHODAS 2.0 was assessed on the day before and three months after the surgery.

Outcomes

The primary outcome of this study was the association between poor recovery on POD 2 and DFS at three months after surgery. Secondary outcomes included the QoR-15 score, severe postoperative complications with a Clavien-Dindo classification of IIIa–V [17], length of postoperative hospital stay, and postoperative 12-item WHODAS 2.0 score.

Statistical analysis

The QoR-15 scores had a normal distribution in this study and are presented as mean ± SDs [12,13]. The other continuous data are presented as medians (Q1, Q3), and categorical variables are presented as numbers (%). The univariate analysis was performed to compare the groups (poor recovery vs. non-poor recovery and DFS vs. non-DFS) using an unpaired t-test (QoR-15 score), Mann-Whitney *U* test, or Fisher's exact test, as appropriate. The primary outcome of this study was evaluated using the Fisher's exact test. The ORs of poor recovery on POD 2 to DFS were calculated using multiple logistic regression analyses with and without adjusting for prominent factors, such as age, preoperative frailty, preoperative DFS, surgical duration, and intraoperative blood loss volume. The ORs of poor recovery to DFS on PODs 4 and 7 were also calculated using multiple logistic regression analysis after adjusting for the same prominent factors. The trajectory of the QoR-15 scores after surgery between patients with and without poor recovery on POD 2 was assessed using a linear mixed model with a random intercept. The effects of poor recovery on POD 2 on postoperative complications, length of postoperative hospital stay, and the postoperative 12-item WHODAS 2.0 scores were compared using univariate analysis. Differences in the mean values for each item of the QoR-15 on POD 2 between patients with and without DFS were also compared using an unpaired t-test.

We estimated that 65% and 85% of patients with and without poor recovery, respectively, would have DFS at three months after surgery. Assuming a ratio of 1 : 3 for each patient group and a dropout rate of 20%, the minimum number of cases required was 260 in this study, with a power of 0.8 and an alpha error of 0.05. All data were analyzed using SPSS version 25.0 (IBM Inc., USA), and statistical significance was set at $P < 0.05$.

Results

During the study period, 260 patients provided informed consent and completed the questionnaires (QoR-15 and 12-item WHODAS 2.0) before surgery. None of the surgeries were postponed or cancelled. Of the 260 patients, 240 completed the questionnaire on POD 2 and 230 completed the follow-up at three months (Fig. 1). Among the 230 patients included in the analysis, the median age was 73.0 years and 70% were male (Table 1).

The mean QoR-15 score on POD 2 was 106.7 (Table 2). According to the QoR-15 score on POD 2, 13.9% (32/230) of patients had excellent recovery, 19.1% (44/230) had good recovery, 39.5% (91/230) had moderate recovery, and 27.3% (63/230) had poor recovery. No statistically significant differences in preoperative and intraoperative characteristics were found between the patients with and without poor recovery on POD 2 (Table 1).

The perioperative mean ± SDs of the QoR-15 scores are shown in Table 2. The patients with poor recovery on POD 2 had lower QoR-15 scores than those without poor recovery on POD 2 at all time points. Fig. 2 shows the postoperative mean QoR-15 scores and 95% CIs for the three time points (POD 2, n = 230; POD 4, n = 226; and POD 7, n = 229). The linear mixed model with repeated measures revealed that the QoR-15 scores increased over time ($P < 0.001$); however, patients with poor recovery on POD 2

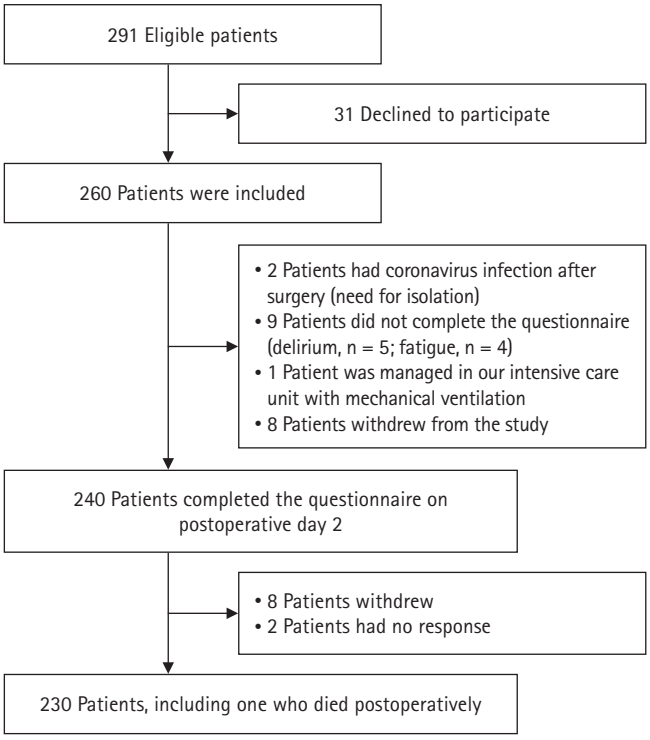

Fig. 1. Flowchart of patient selection.

Table 1. Preoperative and Intraoperative Characteristics

	Total (n = 230)	Non-poor recovery on POD 2 (n = 167)	Poor recovery on POD 2 (n = 63)	P value
Age (yr)	73.0 (69.0, 77.0)	74.0 (69.0, 77.0)	72.0 (69.0, 77.0)	0.250
Sex (Male)	161 (70.0)	120 (71.9)	41 (65.1)	0.336
Height (cm)	163.0 (156.0, 167.0)	162.0 (156.0, 167.0)	163.0 (153.0, 168.0)	0.946
Weight (kg)	60.80 (53.1, 67.3)	60.80 (53.2, 67.4)	60.80 (52.7, 67.0)	0.870
ASA-PS				
1	9 (3.9)	7 (4.2)	2 (3.2)	0.853
2	178 (77.4)	127 (76.0)	51 (81.0)	
3	42 (18.3)	32 (19.2)	10 (15.9)	
4	1 (0.4)	1 (0.6)	0 (0.0)	
Comorbidity				
Symptomatic cerebral vascular disease	12 (5.2)	9 (5.4)	3 (4.8)	0.999
Hypertension	130 (56.5)	95 (56.9)	35 (55.6)	0.882
Ischemic heart disease	18 (7.8)	12 (7.2)	6 (9.5)	0.585
Atrial fibrillation	18 (7.8)	15 (9.0)	3 (4.8)	0.411
Peripheral arterial disease	1 (0.4)	0 (0.0)	1 (1.6)	0.274
Pacemaker or defibrillator	4 (1.7)	3 (1.8)	1 (1.6)	0.999
Asthma	8 (3.5)	4 (2.4)	4 (6.3)	0.219
Diabetes	60 (26.1)	44 (26.3)	16 (25.4)	0.999
Respiratory function				0.789
Normal	145 (63.0)	106 (63.5)	39 (61.9)	
Obstructive lung disease	73 (33.1)	51 (30.5)	22 (34.9)	
Restrictive lung disease	18 (7.8)	14 (8.3)	4 (6.3)	
Medication				
β-blocker	13 (5.7)	8 (4.8)	5 (7.9)	0.351
Steroid	4 (1.7)	3 (1.8)	1 (1.6)	0.999
Statin	63 (27.4)	42 (25.1)	21 (33.3)	0.247
Laboratory data				
Serum albumin (g/dl)	4.20 (4.00, 4.40)	4.20 (4.00, 4.50)	4.20 (4.00, 4.40)	0.993
Serum creatinine (mg/dl)	0.80 (0.68, 0.97)	0.81 (0.69, 0.98)	0.78 (0.68, 0.92)	0.540
Preoperative frailty				0.585
Non-frail	129 (56.0)	97 (58.0)	32 (50.7)	
Prefrail	50 (21.7)	34 (20.3)	16 (25.3)	
Frail	51 (22.1)	36 (21.5)	15 (23.8)	
Preoperative grip-hand strength (kg)	30.80 (23.10, 38.40)	30.80 (24.70, 39.30)	30.80 (21.00, 36.90)	0.260
Mini Nutritional Assessment-short form	13.0 (11.0, 14.0)	13.0 (11.0, 14.0)	12.0 (10.0, 14.0)	0.117
Intraoperative covariate				
Anesthetics agents				0.194
Inhalation agents	223 (97.0)	160 (95.8)	63 (100.0)	
Intravenous agents	7 (3.0)	7 (4.2)	0 (0.0)	
Surgical field				0.119
General	167 (72.6)	116 (69.4)	51 (80.9)	
Urologic	57 (24.7)	45 (26.9)	12 (19.0)	
Gynecologic	6 (2.6)	6 (3.5)	0 (0.0)	
Postoperative analgesia				0.511
None	4 (1.7)	4 (2.3)	0 (0.0)	
PCEA	101 (43.9)	74 (44.3)	27 (42.9)	
IV-PCA	125 (54.3)	89 (53.3)	36 (57.1)	
Surgical duration (min)	290.0 (217.0, 374.0)	276.0 (215.0, 367.0)	330.0 (231.0, 391.0)	0.072
Intraoperative blood loss volume (ml)	66.0 (16.0, 261.0)	60.0 (15.0, 246.0)	100.0 (23.0, 302.0)	0.271

Values are presented as median (Q1, Q3) or number (%). POD: postoperative day, ASA-PS: American Society of Anesthesiologists physical status, PCEA: patient-controlled epidural analgesia, IV-PCA: intravenous patient-controlled analgesia.

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Table 2. Outcome Data of Patients with and without Poor Recovery on POD 2

	Total (n = 230)	Non-poor recovery on POD 2 (n = 167)	Poor recovery on POD 2 (n = 63)	P value
Mean QoR-15 score				
Preoperative	139.7 ± 12.6	141.4 ± 11.7	135.3 ± 13.9	0.001
POD 2	106.7 ± 24.9	118.4 ± 16.6	75.8 ± 14.5	< 0.001
POD 4	118.2 ± 22.5	123.6 ± 20.0	103.6 ± 22.3	< 0.001
POD 7	124.8 ± 21.4	128.4 ± 20.6	115.3 ± 20.6	< 0.001
Number of patients with postoperative complications (Clavien-Dindo classification ≥ IIIa)	16 (6.9)	11 (6.5)	5 (7.9)	0.773
Median length of postoperative hospital stay (days)	9.0 (8.0, 12)	9.0 (7.5, 11.0)	10.0 (8.0, 13.0)	0.165
Median disability score (12-item WHODAS 2.0)				
Preoperative	2.0 (0.0, 8.3)	2.0 (0.0, 8.3)	4.1 (0.0, 12.5)	0.063
3 months postoperative	4.1 (0.0, 14.5)	4.1 (0.0, 12.5)	6.2 (0.0, 29.1)	0.046
Number of patients with disability-free survival				
Preoperative	197 (85.6)	145 (86.8)	52 (82.5)	0.408
3 months postoperative	174 (75.7)	133 (79.6)	41 (65.1)	0.026

Values are presented as mean ± SD, number (%) or median (Q1, Q3). POD: postoperative day, QoR-15: Quality of Recovery-15, WHODAS: World Health Organization Disability Assessment Schedule.

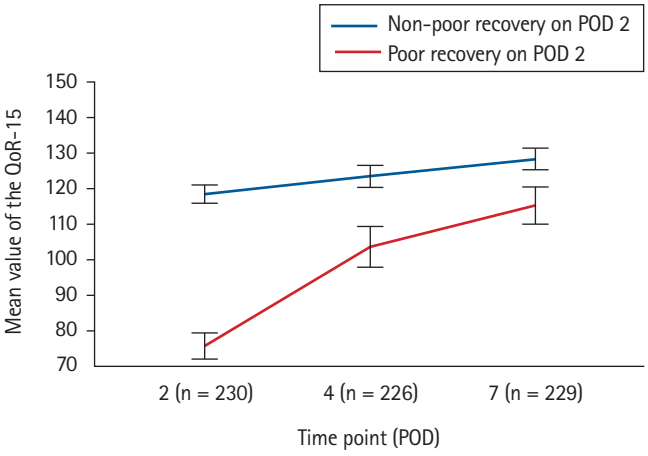

Fig. 2. Comparison of the mean score of the Quality of Recovery-15 (QoR-15) between patients with and without poor recovery on postoperative days (POD) 2, (n = 230), 4 (n = 226), and 7 (n = 229). The linear mixed model includes time points as categorical data with random intercepts and shows that the mean score of the QoR-15 increased over time (POD 4, P < 0.001; POD 7, P < 0.001); however, patients with poor recovery on POD 2 had lower mean scores on the QoR-15 on PODs 4 (P < 0.001) and 7 (P < 0.001) than patients without poor recovery on POD 2.

had lower scores than those without poor recovery at all time points (P < 0.001).

No statistically significant differences in severe postoperative complications (P = 0.773) or the length of postoperative hospital stay (P = 0.165) were found between the two groups (Table 2). Additionally, no statistically significant differences in the proportion of patients who received postoperative chemotherapy (poor recovery group: 28.5% [18/63] vs. non-poor recovery group: 34.1% [57/167], P = 0.442) or postoperative radiotherapy (poor recovery group: 1.5% [1/63] vs. non-poor recovery group: 0.6% [1/167], P = 0.471) were found between the two groups.

The 12-item WHODAS 2.0 scores and number of patients with DFS did not differ significantly between the two groups preoperatively. In contrast, patients with poor recovery on POD 2 had a significantly higher median WHODAS score at three months after surgery compared to patients without poor recovery on POD 2 (6.2 [0.0, 29.1] vs. 4.1 [0.0, 12.5]; P = 0.046) (Table 2). A greater number of patients without poor recovery on POD 2 (79.6%) than those with poor recovery on POD 2 (65.1%) had DFS at three months after surgery (P = 0.026) (Table 2). The OR of poor recovery on POD 2 to DFS at three months after surgery was 0.481 (95% CI [0.233, 0.994]), even after adjusting for relevant factors (Table 3). Two of the patients who underwent postoperative radiotherapy also received chemotherapy; thus, only postoperative chemotherapy was included as a postoperative covariate for multiple analysis.

Additionally, poor recovery on PODs 4 and 7 was not associated with DFS at three months after surgery (Supplementary Table 1).

Among the QoR-15 items on POD 2, breathing (P = 0.001), rest (P = 0.016), well-being (P = 0.022), moderate pain (P = 0.010), severe pain (P < 0.001), and depression (P = 0.004) were significantly different between patients with and without DFS three months after surgery (Supplementary Table 2).

Table 3. Odds Ratio for the Association between Poor Recovery on POD 2 and DFS at Three Months after Surgery

	Unadjusted estimated		Adjusted estimated	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Poor recovery on POD 2	0.476 (0.251, 0.904)	0.023	0.481 (0.233, 0.994)	0.048

The adjusted model was adjusted for age, preoperative frailty, preoperative DFS, surgical duration, intraoperative blood loss volume, and postoperative chemotherapy. The area under the curve was 0.763 (95% CI: 0.684, 0.841; Hosmer-Lemeshow, P = 0.867). POD: postoperative day, DFS: disability-free survival.

Discussion

This study showed that, according to QoR-15 scores, patients with poor recovery on POD 2 had a decreased likelihood of DFS at three months after surgery compared to patients without poor recovery, with an OR of 0.483 after adjusting for baseline risk and surgical factors. Furthermore, although patients with poor recovery on POD 2 had lower perioperative QoR-15 scores, poor recovery was not significantly associated with postoperative complications or length of postoperative hospital stay.

Although surgery contributes to life support and functional recovery, not all patients benefit from surgery. In this study, the incidence of DFS at three months after surgery was 75.7% (174/230), a decrease from the estimated rate preoperatively (85.6% [197/230]). Although this incidence was not compared to previous studies using different definitions (WHODAS scores < 25%), the high prevalence of patients without DFS is a considerable social concern that would need to be addressed after discharge. Although preoperative frailty is a well-known factor associated with postoperative functional disability, it is not necessarily optimized preoperatively. Thus, early postoperative detection of factors affecting mid-term functional disability is essential. The only immediate postoperative factor associated with DFS that has been reported to date is anemia [9,18,19]; thus, this study provides new evidence that poor immediate postoperative recovery is a predictor of DFS.

Patients with poor recovery on POD 2 had lower QoR-15 scores on PODs 4 and 7 than those without poor recovery on POD 2; however, poor recovery on PODs 4 and 7 were not associated with DFS at three months after surgery. This may be explained by the limited number of patients with poor recovery on POD 4 (n = 28) and POD 7 (n = 12). Regardless, accurately identifying patients who are likely to have poor outcomes after hospital discharge is essential. Although we also evaluated QoR-15 scores preoperatively in this study, the QoR-15 was developed for postoperative assessment and the preoperative score does not necessarily reflect the patient's baseline score; thus, we did not include the preoperative QoR-15 scores in this analysis [3,14]. Six of the QoR-15 items (breathing, rest, well-being, moderate pain, severe pain, and depression) showed differences between the patients with and without DFS at three months after surgery. Previous studies have shown that well-controlled pain after abdominal surgery leads to better postoperative recovery [20–22]; therefore, providing strategies to control postoperative pain and optimize mental status can contribute to an increase in DFS.

Two previous studies found an association between the severity of postoperative recovery classified according to the QoR-15 score and postoperative complications, which is not consistent with the findings of this study [10,14]. This could be explained by the following: (1) these studies included relatively minor complications (e.g., additional opioids for pain control), while our study only included severe complications (Clavien-Dindo classification IIIa–V) and (2) our sample size may not have been large enough to detect this association.

This study had some limitations. First, we could not demonstrate a causal relationship between poor postoperative recovery and DFS three months after surgery owing to the observational nature of the study. Second, although factors after hospital discharge may affect DFS, detecting patients at risk of not achieving DFS early allows for the initiation of timely and appropriate interventions. Finally, because this was a single-center study involving only patients who underwent major abdominal surgery, the generalizability of our findings may be limited.

In conclusion, we found that patients with poor recovery on POD 2, as defined using the QoR-15, were more likely to not have DFS at three months after abdominal surgery. These findings may allow for early and effective interventions to be initiated based on each patient's condition after abdominal surgery.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

Yuki Kinugasa (Conceptualization; Data curation; Investigation; Writing – original draft)
Mitsuru Ida (Conceptualization; Formal analysis; Methodology; Visualization; Writing – original draft)
Shohei Nakatani (Investigation; Writing – review & editing)
Kayo Uyama (Investigation; Writing – review & editing)
Masahiko Kawaguchi (Conceptualization; Supervision; Writing – review & editing)

Supplementary Materials

Supplementary Table 1. Odds ratio for the association between poor recovery on PODs 4 and 7 and DFS at 3 months.
Supplementary Table 2. Mean QoR-15 scores on POD 2 between patients with and without DFS at 3 months after surgery.

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Comparison of the pericapsular nerve group block with the intra-articular and quadratus lumborum blocks in primary total hip arthroplasty: a randomized controlled trial

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Background: The pericapsular nerve group (PENG) block, quadratus lumborum block (QLB), and intra-articular (IA) local anesthetic injection have been shown to provide effective analgesia in total hip arthroplasty (THA). This randomized study aimed to compare the analgesic efficacy, motor protection, and quality of recovery associated with the PENG block, QLB, and IA injection.

Methods: Eighty-nine patients who underwent a unilateral primary THA under spinal anesthesia were randomly assigned to the PENG (n = 30), QLB (n = 30), or IA (n = 29) group. The primary outcome was the numerical rating scale (NRS) score over the first 48 h postoperatively. The secondary outcomes were postoperative opioid consumption, quadriceps and adductor muscle strength, and quality of recovery (QoR-40).

Results: The dynamic (with movement) NRS scores at 3 and 6 h postoperatively were significantly lower in the PENG and QLB groups compared to the IA group (P = 0.002 and P < 0.001, respectively). The time to first opioid analgesia requirement was longer in the PENG and QLB groups than in the IA group (P = 0.009 and P = 0.016, respectively). A provided better preservation was found in the the PENG group than in the QLB group in terms of quadriceps muscle strength at 3 h postoperatively (P = 0.007) and time to mobilization (P = 0.003). No significant differences in the QoR-40 scores were seen.

Conclusions: The PENG and QLB groups showed similar analgesic effects and both showed more effective analgesia 6 h postoperatively than the IA group. All the groups showed similar postoperative quality of recovery.

Keywords: Anesthesia; Arthroplasty; Lower extremity; Nerve block; Pain management; Postoperative pain.

Introduction

As the hip joint receives sensory innervation from both the lumbar and sacral plexuses, providing effective regional analgesia to this area is difficult [1]. Additionally, the method used for postoperative analgesia after hip surgery must both provide effective analgesia and allow for mobilization as early as possible [1,2]. Ideally, this process should also have a motor protective effect to reduce the risk of thromboembolic events and increase functional improvement by shortening the length of hospital stay [3].

The pericapsular nerve group (PENG) block described in 2018 by Giron-Arango et al. [4] can be used for hip surgery. In hip fracture surgery and elective arthroplasty, a preop-

erative and postoperative analgesic blockade is applied to the obturator, femoral, and accessory obturator nerves, which innervate the anterior side of the hip joint [5]. With the PENG block, only the sensory branches of the femoral nerve that travel to the hip joint are blocked; no motor blockade occurs [6]. Consequently, excellent analgesia can be provided without affecting muscle strength, which facilitates postoperative functional recovery.

The quadratus lumborum block (QLB), first described by Blanco [7] in 2007, is administered around the quadratus lumborum muscle (QLM). The QLM is located between the middle and anterior thoracolumbar fascia adjacent to the fascia of the psoas major muscle (PM) medially and the transversalis fascia laterally. The name changes according to the point of injection [8–10]. In earlier studies, the anterior QLB was also classified as the transmuscular approach (between the QLM and PM) [11]. Owing to its anatomical proximity to the QLM, the QLB is thought to have a large blocking capacity through affecting the L1-3 nerve root. Cadaveric studies have shown that the anterior and subcostal QLB cover nerves that provide sensory innervation to the hip [8,9]. The QLB has also been shown to provide effective analgesia for total hip arthroplasty (THA) without causing weakness in the quadriceps muscles [10].

Intra-articular (IA) local anesthetic injections, which are practical and easy to administer, have been reported to result in lower postoperative pain scores and opioid compared to non-administered group in previous studies on hip arthroplasty [12,13].

We hypothesized that patients undergoing THA who received the PENG block would have lower numerical rating scale (NRS) scores and opioid consumption and better motor protection and quality of recovery (QoR) than those who received the QLB and IA injection. The primary outcome of this prospective randomized study was the severity of pain represented by the NRS score of patients undergoing THA, measured in the first 48 h after receiving the PENG block, QLB, and IA injection. The secondary outcomes included postoperative opioid consumption, time to first mobilization, quadriceps muscle strength, hip adduction strength, and QoR (according to the QoR-40).

Materials and Methods

The study protocol was approved by the Ethics Committee of Karamanoğlu Mehmetbey University Faculty of Medicine (decision no: 04-2021/14, June 23, 2021). This trial was registered at ClinicalTrials.gov (NCT05003544). Written informed consent was obtained from all patients who participated in the study, in accordance with the principles of the Declaration of Helsinki, 2013.

Patients aged 18–85 years who underwent unilateral primary THA with spinal anesthesia administered in accordance with the American Society of Anesthesiologists (ASA) I–III criteria between August 12, 2021 and January 31, 2023 were included in the study. The exclusion criteria were as follows: a history of surgery on the same hip, liver or kidney failure, allergy or intolerance to one of the study drugs, body mass index > 40 kg/m^2, ASA phsyical status score of IV, or long-term use of gabapentin/pregabalin or opioids.

Patient randomization was performed at a ratio of 1 : 1 : 1 basis by an expert who was not involved in the study using a computer-generated program (https://www.randomizer.org). Patients were assigned to one of three groups (30 patients each) using computer-generated random numbers and coded sealed opaque envelopes that were opened immediately before performing the PENG block (PENG group), QLB (QLB group), or IA injection (IA group). A specialist who did not perform the preoperative block and was blinded to the patient groups performed the postoperative evaluation. The postoperative pain assessment specialists, nurses, and patients were all blinded to the intervention group, including during the data collection process.

As part of the multimodal analgesia, 1,000 mg paracetamol was administered intravenously (IV) in the preoperative holding area. Patients were followed up in a standard manner. Subsequently, 2 mg IV midazolam, 40 mg IV esomeprazole, and 4 mg IV dexamethasone were administered. After the patients were positioned appropriately for spinal anesthesia, 2.2 ml of 0.5% hyperbaric bupivacaine was injected into the L3-4 intervertebral space. The posterolateral surgical approach was used in all patients in the lateral decubitus position.

For postoperative analgesia, patients were routinely administered 1,000 mg IV paracetamol three times a day and 50 mg oral diclofenac every 8 h (25 mg if aged ≥ 75 years). In addition, 5 mg oral oxycodone was administered to patients with an NRS score > 4.

Sham procedure

The sham block procedure was applied to all patient groups. When applying the sham procedure, the QLB and PENG block protocols were performed using a simulation method. The simulation QLB was applied to the PENG group, the PENG simulation to the QLB group, and both block simulation the IA group. The practitioner simulated these blocks after the QLB and PENG block positions were assigned to all participating patients. After probe placement in a QLB- and PENG block-like manner, a sufficient pause was allowed to simulate a blunt needle, then a 20 ml syringe with saline, without administering any medication.

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PENG block technique

For the PENG block, sterile conditions were maintained with the patient in the supine position. A low-frequency convex ultrasound transducer (Samsung RS85 Prestige®, Republic of Korea) was placed in the anteroinferior iliac spine. The probe was placed a transverse orientation, medical, and caudal to the anterosuperior iliac spine in order to identify the anteroinferior iliac spine, the iliopubic eminence, and the psoas tendon. After the psoas tendon was visualized, with a 21-gauge 100-mm block needle (B. Braun®, Germany), the tip of the psoas tendon was determined using the in-plane technique with a lateral-to-medial approach (Fig. 1A). Following negative aspiration, 20 ml of 0.5% bupivacaine was injected under the psoas tendon and local anesthetic spread was observed (Fig. 1B).

QLB technique

For the anterior QLB, the patients were positioned laterally with the surgical side facing up. A low-frequency convex ultrasound probe was placed at the level of the L4 spine with the iliac wing. When the "Shamrock" appearance (Fig. 2A) was visualized, a 21-gauge 100-mm block needle was advanced to the QLM in the posterior to anterior direction using the in-plane technique and the needle tip was inserted between the PM and the fascial space of the QLM. Following negative aspiration, 30 ml of 0.5% bupivacaine was slowly injected into the fascial area (Fig. 2B). Block success was confirmed by observing the separation of the QLM and PM in the same plane.

IA injection

After the placement of the hip prosthesis, 30 ml of 0.5% bupivacaine and 30 ml of saline were administered by IA injection after the joint capsule was closed.

Outcome measurements

The primary outcome measure was the maximum severity of pain perceived at all postoperative time points (3, 6, 8, 12, 24, and 48 h) using an NRS pain score ranging from 0–10. The NRS value was evaluated as rest (static) and during movement (dynamic) for the first 48 h postoperatively.

The secondary outcomes were the time to first postoperative opioid requirement and opioid consumption (reported in oral morphine equivalents within the first 48 h postoperatively). Quadriceps motor function was evaluated at 3, 6, 12, and 24 h postoperatively with the hip and knee flexion test at 45° and 90°, respectively (normal strength = 0 points [extension against resistance]; paresis = 1 point [flexion against gravity but not against resistance]; and paralysis = 2 points [no extension]). An inflated blood pressure cuff was placed at 40 mmHg of hip adduction force and the patient was instructed to compress the cuff as hard as possible and maintain this effort. The percent reduction in

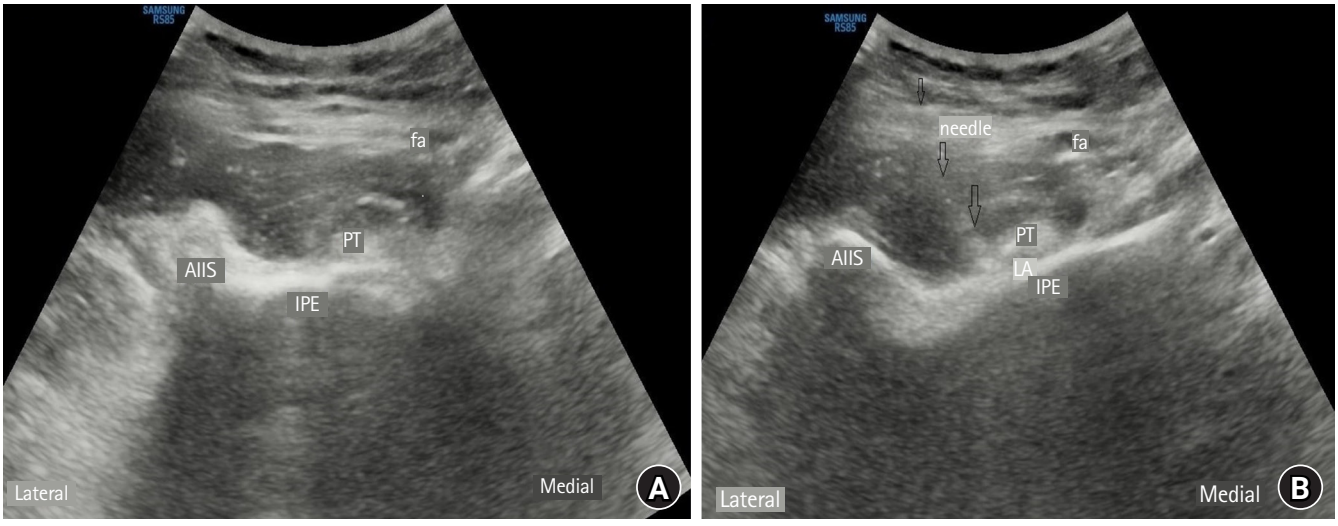

Fig. 1. Pericapsular nerve group block. (A) A low-frequency curvilinear was placed in a transverse orientation, medial and caudal to the anterosuperior iliac spine in order to identify the anterior inferior iliac spine, the iliopubic eminence, and the psoas muscle tendon. (B) The needle placement between the psoas muscle tendon and the iliopubic eminence with a lateral-to-medial approach using the in-plane technique. After negative aspiration, local anesthetic spread was observed under the psoas muscle tendon. AIIS: anterior inferior iliac spine, fa: femoral artery, IPE: iliopubic eminence, PT: psoas muscle tendon, LA: local anesthesia.

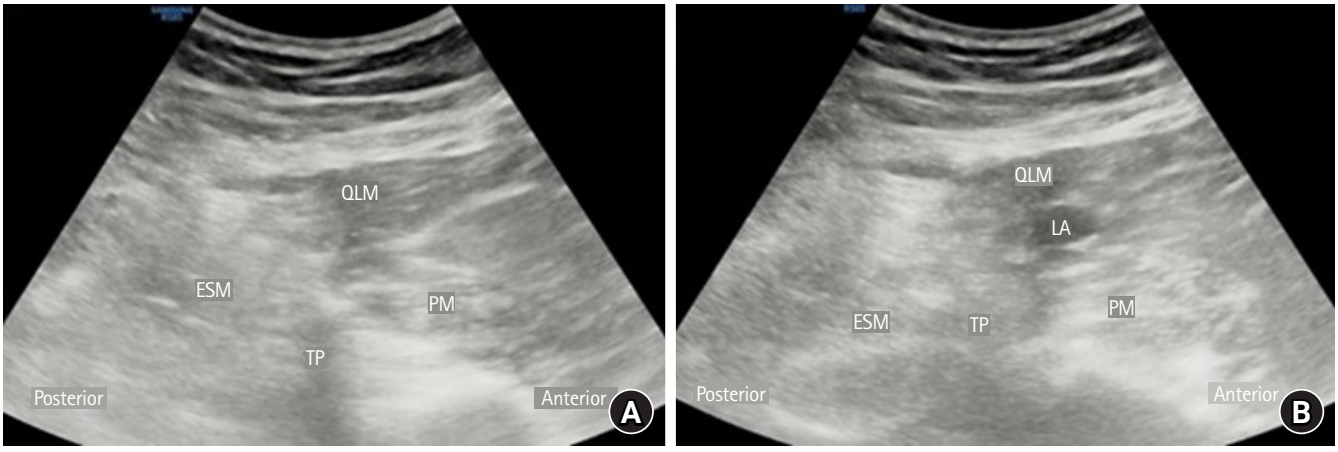

Fig. 2. Anterior quadratus lumborum block. (A) A low-frequency convex ultrasound probe was placed at the level of the L4 spine with the iliac wing. Subsequently, the L4 vertebral body at the L4 vertebra level, along with the L4 transverse process, the quadratus lumborum, the erector spinae muscle, and the psoas muscle, were identified as the Shamrock sign. (B) The needle placement between the QLM and the psoas muscle with a posterior-to-anterior approach using the in-plane technique. After negative aspiration, local anesthetic spread was observed between the QLM and the psoas muscle. QLM: quadratus lumborum muscle, ESM: erector spinal muscle, PM: psoas muscle, TP: transverse process, LA: local anesthesia.

strength compared with the baseline measurement was scored as follows: 0%–20% = 0 points, 21%–70% = 1 point, and 71%–90% = 2 points [14,15]. QoR was evaluated on postoperative days 1, 2, and 7 using the QoR-40 questionnaire. The development of nausea, vomiting, pruritus, urinary retention, or respiratory depression was recorded, and patient satisfaction was evaluated.

Statistical analysis

The sample size was calculated for the one-way analysis of variance (ANOVA), which was used to test the main hypothesis of the study (comparison of NRS scores between the three independent groups). Before starting the study, a power analysis was performed with reference to the literature [16] and expert opinion. The effect size was calculated using the mean postoperative (0–12 h) NRS values obtained from the literature (the mean NRS values of the PENG and control groups were 2.5 and 5.5, respectively; the mean NRS value of the QLB was estimated to be 4 based on expert opinion; and standard deviations were homogeneous and the mean was 3) [16,17]. Cohen's effect size was calculated as 0.408 using the group mean and standard deviation values. To reach a minimum power of 90% ($1-\beta = 0.10$) with $\alpha = 0.05$ error (95% confidence interval, CI) for the ANOVA test, the minimum number of patients to include in the study was determined to be 81 (27 patients in each group). Considering a potential loss to follow-up for any reason of 10%, 90 patients (30 patients in each group) were included in the study. G*Power (version 3.1.9.5; Heinrich-Heine-Universität, Germany) was used for sample size estimation.

Statistical data analyses were conducted using IBM® SPSS® Statistics software (version 22; IBM Corp., USA). Descriptive categorical data are presented as numbers (n) and percentages (%). The chi-square or Fisher's exact test was used, depending on the sample sizes in the crosstab cells, to compare the ratios between categorical variables. Descriptive statistics of numerical data are presented as mean ± standard deviation or median (Q1, Q3) values, depending on whether the data were normally distributed. The Shapiro-Wilk test and some graphical methods (histogram and Q-Q plots) were used to determine the conformity of the data to a normal distribution. One-way ANOVA was used to compare normally distributed numerical data among the three independent groups, and the Kruskal-Wallis test was used to compare non-normally distributed data.

For comparisons showing significant differences in the ANOVA, the Tukey test was conducted, and the Kruskal-Wallis test was followed by Dunn-Bonferroni post-hoc pairwise comparison tests. A two-way mixed ANOVA was used as parametric test. The effect of the research groups on the change in the repeated measurements of NRS values at rest (static) and during movement (dynamic) measured at seven different time points (Supplementary Material 1). All statistical tests were two-sided, and the level of statistical significance was set at $P < 0.05$.

Results

A total of 112 patients were screened, and 22 were excluded from the study. After completing randomization, one patient in

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the IA group was excluded because of unsuccessful spinal anesthesia. A total of 89 patients were thus analyzed: 30 in the PENG group, 30 in the QLB group, and 29 in the IA group (Fig. 3). The demographic and clinical characteristics of the study groups are shown in Table 1.

A comparison of the static and dynamic NRS scores between the groups is presented in Table 2. According to the post-hoc test results, the dynamic NRS scores of the PENG (0.37 ± 0.80) and QLB (0.63 ± 0.85) groups 3 h postoperatively were significantly lower from those of the IA (1.38 ± 1.54) group (P = 0.002, P = 0.036, respectively). Both the static and dynamic NRS scores of the IA group (static: 2.00 ± 1.03, dynamic: 4.07 ± 1.66) 6 h postoperatively were significantly higher from those of the PENG (static: 1.20 ± 0.92, dynamic: 2.43 ± 1.45; P = 0.005, P < 0.001, respectively) and QLB groups (static: 1.30 ± 0.87, dynamic: 2.83 ± 0.74; P = 0.017, P = 0.002, respectively) (Table 2). Intra- and inter-group comparisons of the static and dynamic NRS scores measured at the seven time points are presented in Supplementary Tables 1 and 2.

The post-hoc test results showed a significant difference in the time to first opioid requirement in the IA group compared to the PENG and QLB groups (7 [5, 8], 10.5 [7.75, 14], and 11 [5.75, 14.25]; P = 0.009 and P = 0.016, respectively). The analgesic requirement between 0 and 6 h in the PENG group was significantly different from that in the IA group (0 [0, 0] vs. 0 [0, 7.5]; P = 0.032). In the total time evaluated (0–48 h), only the amount of analgesic requirement in the IA group was significantly higher than that in the QLB group (7.5 [7.5, 15] and 15 [11.25, 22.5]; P = 0.040) (Table 3).

The distribution of the quadriceps muscle strength rates at 3 h was significantly different between the PENG (23.3%) and QLB (63.3%) groups (P = 0.019) (Table 4). According to the post-hoc test results, the quadriceps muscle strength at 3 h postoperatively in the QLB group was significantly lower than that in the PENG group (P = 0.007).

A statistically significant difference was observed in the time to mobilization between the study groups (P = 0.011) (Table 5). According to the post-hoc test results, the time to mobilization in

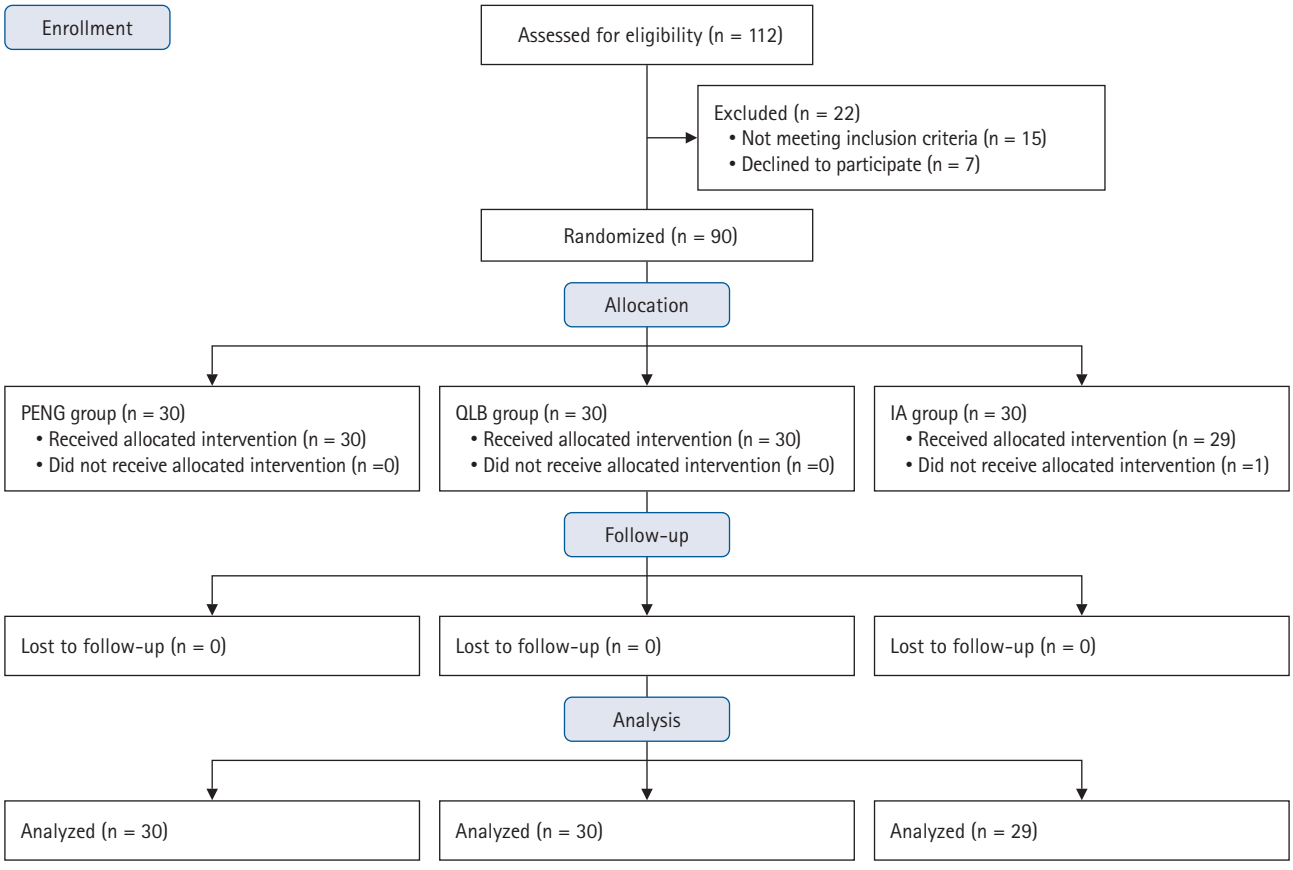

Fig. 3. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. PENG: pericapsular nerve group, QLB: quadratus lumborum block, IA: intra-articular injection.

Table 1. Comparison of Demographic and Clinical Characteristics among the Study Groups

Variable	PENG group (n = 30)	QLB group (n = 30)	IA group (n = 29)	P value
Gender				
Female	17 (56.7)	18 (60.0)	16 (55.2)	0.929*
Male	13 (43.3)	12 (40.0)	13 (44.8)	
Age (yr)	68.83 ± 11.10	72 ± 11.40	68.52 ± 13.10	0.460
BMI (kg/m^2)	29.01 ± 4.06	30.20 ± 3.97	30.39 ± 3.75	0.344
ASA score				
1	5 (16.7)	3 (10.0)	5 (17.2)	0.641†
2	18 (60.0)	21 (70.0)	21 (72.4)	
3	7 (23.3)	6 (20.0)	3 (10.3)	
Perioperative diagnosis				
Fracture	16 (53.3)	12 (40.0)	11 (37.9)	0.430*
No fracture	14 (46.7)	18 (60.0)	18 (62.1)	
Surgical side				
Left	14 (46.7)	18 (60.0)	17 (58.6)	0.522*
Right	16 (53.3)	12 (40.0)	12 (41.4)	
Duration of anesthesia	109.90 ± 10.90	109.10 ± 14.20	111.0 ± 10.90	0.840
Duration of surgery	87.40 ± 13.10	84.70 ± 15.86	91.86 ± 12.65	0.145
Preoperative NRS score	5.67 ± 1.47	5.43 ± 1.33	6.07 ± 1.36	0.213

Values are presented as number (%) or mean ± SD. PENG: pericapsular nerve group block, QLB: quadratus lumborum block, IA: intra-articular injection, BMI: body mass index, ASA: American Society of Anesthesiologists, NRS: numerical rating scale. *Chi-square test with n (%), †Fisher's exact test with n (%), ANOVA with mean ± SD values.

Table 2. Comparison of Static and Dynamic NRS Scores among the Study Groups

Time	3 h	6 h	8 h	12 h	24 h	48 h
Static						
PENG* (n = 30)	0.17 ± 0.46	1.20 ± 0.92	2.27 ± 0.69	2.87 ± 1.07	1.80 ± 1.03	0.93 ± 0.86
QLB† (n = 30)	0.30 ± 0.70	1.30 ± 0.87	2.23 ± 0.67	2.63 ± 0.71	1.57 ± 0.89	0.87 ± 0.93
IA‡ (n = 29)	0.55 ± 0.91	2.00 ± 1.03	2.52 ± 0.78	2.59 ± 1.08	1.66 ± 0.93	0.62 ± 0.67
P value	0.115	0.003§	0.261	0.496	0.636	0.325
Post hoc P value	-	*,†1.000 *,‖0.005§ †,‡0.017§	-	-	-	Interaction effect F (12;516) = 1.921, P = 0.030§
Dynamic						
PENG* (n=30)	0.37 ± 0.80	2.43 ± 1.45	4.10 ± 1.26	4.53 ± 1.47	3.07 ± 1.08	2.37 ± 0.80
QLB† (n=30)	0.63 ± 0.85	2.83 ± 0.74	3.90 ± 1.34	4.53 ± 1.61	2.87 ± 1.07	2.43 ± 0.72
IA‡ (n=29)	1.38 ± 1.54	4.07 ± 1.66	4.62 ± 1.76	4.66 ± 1.89	3.03 ± 1.52	2.14 ± 0.69
P value	0.002§	< 0.001§	0.159	0.949	0.800	0.287
Post hoc P value	*,†1.000 *,‡0.002§ †,‡0.036§	*,†0.757 *,‡< 0.001§ †,‡0.002§	-	-	-	Interaction effect F (12;516) = 2.306, P = 0.007§

Values are presented as mean ± SD (or SEM). *PENG: pericapsular nerve group, †QLB: quadratus lumborum block, ‡IA: intra-articular injection. §P value < 0.05; statistically significant.

the QLB group was significantly longer than that in the PENG group (17.3 ± 4.92 and 13.17 ± 4.43; P = 0.003). No significant differences were observed between the groups with respect to the QoR-40 score, patient satisfaction, or complications (Table 5).

Discussion

The results of this randomized controlled study demonstrated that the PENG block and QLB provided more effective analgesia

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Table 3. Comparison of the Required Oral Morphine Equivalents among the Study Groups

Morphine consumption	PENG group* (n = 30)	QLB group† (n = 30)	IA group‡ (n = 29)	P value	Post hoc P values
Time to first opioid requirement (h)	10.5 (7.75, 14)	11.0 (5.75, 14.25)	7.0 (5, 8)	0.004§	*,†1.000
					*,‡0.009§
					†,‡0.016§
0, 6 h (mg)	0 (0, 0)	0 (0, 0)	0 (0, 7.5)	0.021§	*,†1.000
					*,‡0.032§
					†,‡0.074
6, 12 h (mg)	0 (0, 7.5)	0 (0, 7.5)	7.5 (0, 7.5)	0.055	-
12, 24 h (mg)	7.5 (5.62, 7.5)	7.5 (0, 7.5)	7.5 (0, 7.5)	0.353	-
24, 48 h (mg)	0 (0, 1.87)	0 (0, 0)	0 (0, 0)	0.819	-
Total (0, 48 h) (mg)	15.0 (7.5, 15)	7.5 (7.5, 15)	15.0 (11.25, 22.5)	0.037§	*,†1.000
					*,‡0.194
					†,‡0.040§

Values are presented as median (Q1, Q3). *PENG: pericapsular nerve group, †QLB: quadratus lumborum block, ‡IA: intra-articular injection. §P < 0.05; statistically significant.

Table 4. Comparison of Quadriceps Muscle Strength and Hip Adduction Strength among the Study Groups

Variable		PENG group (n = 30)	QLB group (n = 30)	IA group (n = 29)	P value
Quadriceps muscle strength					
3 h	Normal	9 (30.0)	5 (16.7)	5 (17.2)	0.019*,†
	Paresis	14 (46.7)	6 (20.0)	14 (48.3)	
	Paralysis	7 (23.3)	19 (63.3)	10 (34.5)	
6 h	Normal	18 (60.0)	9 (30)	16 (55.2)	0.053‡
	Paresis	10 (33.3)	14 (46.7)	12 (41.4)	
	Paralysis	2 (6.7)	7 (23.3)	1 (3.4)	
12 h	Normal	24 (80.0)	22 (73.3)	26 (89.7)	0.277†
	Paresis	6 (20.0)	8 (26.7)	3 (10.3)	
	Paralysis	-	-	-	
24 h	Normal	30 (100)	30 (100)	29 (100)	1.000‡
	Paresis	-	-	-	
	Paralysis	-	-	-	
Hip adduction strength					
3 h	0–20	13 (43.3)	21 (70.0)	12 (41.4)	0.091‡
	21–70	13 (43.3)	6 (20.0)	15 (51.7)	
	71–90	4 (13.4)	3 (10.0)	2 (6.9)	
6 h	0–20	3 (10.0)	5 (16.7)	1 (3.4)	0.159‡
	21–70	14 (46.7)	18 (60.0)	13 (44.8)	
	71–90	13 (43.3)	7 (23.3)	15 (51.7)	
12 h	0–20	-	-	-	0.123†
	21–70	7 (23.3)	11 (36.7)	4 (13.8)	
	71–90	23 (76.7)	19 (63.3)	25 (86.2)	
24 h	0–20	-	-	-	0.326‡
	21–70	0 (0.0)	2 (6.7)	0 (0.0)	
	71–90	30 (100)	28 (93.3)	29 (100)	

Values are presented as number (%). PENG: pericapsular nerve group, QLB: quadratus lumborum block, IA: intra-articular injection. *P < 0.05; statistically significant, †Chi-square test with n (%), ‡Fisher's exact test with n (%).

Table 5. Comparison of Postoperative Quality of Recovery (based on the QoR-40), Patient Satisfaction, Time to Mobilization, and Complications among the Study Groups

Variable	PENG group (n = 30)	QLB group (n = 30)	IA group (n = 29)	P value
Patient satisfaction				
Yes	21 (70.0)	22 (73.3)	20 (69.0)	0.928†
No	9 (30.0)	8 (26.7)	9 (31.0)	
Time to mobilization (h)	13.17 ± 4.43	17.30 ± 4.92	15.31 ± 6.11	0.011*
QoR-40 score				
24 h	170 (163, 179)	174 (168.7, 178)	174 (170, 179.5)	0.141
48 h	192.5 (188.7, 194.2)	192.5 (190, 194)	192.0 (189, 194.5)	0.886
1 wk	197 (195, 198)	197 (195.7, 197)	197 (196, 197)	0.473
Nausea				
No	28 (93.3)	28 (93.3)	22 (75.9)	0.064†
Yes	2 (6.7)	2 (6.7)	7 (24.1)	
Vomiting				
No	29 (96.7)	28 (93.3)	28 (96.6)	0.786‡
Yes	1 (3.3)	2 (6.7)	1 (3.4)	
Pruritus				
No	29 (96.7)	30 (100)	29 (100)	1.000‡
Yes	1 (3.3)	0 (0.0)	0 (0.0)	
Urinary retention				
No	29 (96.7)	30 (100)	29 (100)	1.000‡
Yes	1 (3.3)	0 (0.0)	0 (0.0)	
Respiratory depression				
No	30 (100)	30 (100)	29 (100)	1.000‡
Yes	0 (0.0)	0 (0.0)	0 (0.0)	

Values are presented as mean ± SD (or SEM) or median (Q1, Q3). PENG: pericapsular nerve group, QLB: quadratus lumborum block, IA: intra-articular injection, QoR: quality of recovery. *P < 0.05; statistically significant. †Chi-square test with n (%), ‡Fisher's exact test with n (%), ANOVA test with mean ± SD values, Kruskal-Wallis test with median value (Q1, Q3).

for up to 6 h postoperatively than IA local anesthetic injections. QLBs and PENG blocks showed similar analgesic effects. The PENG block and QLB were more effective than the IA injection in terms of the time to first analgesia requirement. The PENG block was also found to be more effective at enabling early mobilization than the QLB, as it provided motor-protective analgesia up to 3 h postoperatively. Although the QLB had a similar effect to the PENG block with respect to 48-h opioid consumption, the QLB group was associated with less opioid consumption than the IA group. Despite the analgesic effects of the PENG block and QLB and the motor-protective effect of the PENG block, the three applications had a similar postoperative effect on the QoR.

Due to the complex innervation of the hip joint, the importance placed on regional anesthesia to provide adequate analgesia in THA is increasing. The presence of a large number of mechanoreceptors and nociceptors in the anterior capsule and innervation by the femoral and obturator nerves are the primary sources of pain in the hip joint [18]. Studies have shown that adequate analgesia is achieved with the PENG block as it effectively blocks the femoral, obturator, and accessory obturator nerves, which innervate the anterior capsule [16]. However, some studies have reported that the analgesic efficacy of PENG block for THA is limited and shown no evidence for the expected analgesic effect [14,19].

Cadaveric studies have found that the anterior QLB spreads to the lumbar plexus and paravertebral space, with wide dermatomal spread in the T7–L2 range [20]. Another recent cadaveric study showed that the anterior (transmuscular) QLB consistently spreads to the lumbar nerve roots and subcostal nerves compared with lateral QLB and posterior QLB [9]. Due to infiltration from the QLM and PM, spread of the QLB to the ilioinguinal, iliohypogastric, lateral cutaneous femoral nerves, genitofemoral nerve, and obturator nerves differs [21]. Another cadaveric study and case series demonstrated that the suprailiac approach to the anterior QLB includes T10–L3 dermatomal coverage [8]. Kukreja et al. [10] reported that the anterior QLB provided effective postoperative THA analgesia in the first 48 h postoperatively and re-

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duced opioid consumption.

In a study comparing the combination of the PENG block and QLB with the PENG block alone for hip revision surgeries, lower pain scores were observed in the combination group for the first 12–24 h [22].

These differing results for the QLB in cadaveric studies are due to the widespread area and the inability to predict the distribution pattern of local anesthesia. Furthermore, given the deep location of the QLM and the adjacent retroperitoneal and abdominal organs, the clinical use of the QLB is limited. Other factors that limit its use include the need for advanced technical skill and considerable attention to detail [20]. In the current study, both the QLB and PENG block provided similar analgesic effects, but the PENG block was more effective in terms of opioid consumption in the first 6 h postoperatively. Although the advantages of the PENG block include ease of implementation technically with patient positioning, the limited duration of analgesia for hip surgery may be a disadvantage.

As demonstrated in previous studies, administration of the PENG block [16], QLB [10], or IA injection [12,13] alone contributes to a reduction in postoperative pain scores and opioid consumption in patients undergoing THA. To the best of our knowledge, however, this is the first randomized controlled study to compare these three techniques. In a study by Pascarella et al. [16], the PENG block was found to significantly reduce the 48-h NRS values; however, as the intervention group could not be blinded, a strong postoperative evaluation could not be made. Another recent study emphasized that adding a PENG block to IA injection under general anesthesia does not contribute to the analgesic effect [19]. For the current study, spinal anesthesia was administered to limit high-dose opioid use intraoperatively. Opioid-induced hyperalgesia and opioid tolerance, which may occur following the use of short-acting opioids, were therefore avoided. The current study results showed that the PENG block significantly reduced NRS scores, and opioid consumption was lower at 6 h compared to IA local anesthetic injection.

Femoral, fascia iliaca, and epidural blocks cause delays in mobilization [23]. As a result, length of hospital stay is prolonged, and complications may develop. One recent study concluded that the motor-protective effect of the PENG block was superior to that of the suprainguinal fascia iliaca block [14]. Another study comparing the PENG and femoral blocks in patients with femoral fractures found that the PENG block was better at preserving quadriceps strength. However, it has also been shown that, because of the medial spread of a high amount of local anesthesia, the PENG block can cause obturator motor blockade [24]. Although the current study results showed that motor function was well preserved with the PENG block in the first 3 h postoperatively compared to the QLB, no difference was found at the other evaluation times. Given that patients undergoing the PENG block have a shorter time to mobilization, this block is more frequently preferred for early mobilization [14,25]. Additionally, unpredictable nerve root involvement may occur as a result of the QLB spreading in the fascial compartments and covering a wide network of nerves.

No difference was found among the three methods used in this study with respect to postoperative patient satisfaction or QoR scores. Earlier patient mobilization has been associated with fewer complications, lower mortality rates and pain scores, and shorter lengths of hospital stay [26,27]. Although the PENG block provided effective analgesia only at some of the evaluation points, the associated earlier mobilization increased clinicians' preference for this block, especially in the fragile eldery patient group.

This study had some limitations. First, no normal control group was included. The presence of a control group is essential to evaluate the effectiveness of a given block. Nevertheless, data from previous studies showed that a sham or placebo group would be unlikely to change the clinical interpretation of these results. Although the study was planned to be prospective and randomized, the patients may not have been completely blinded because they were awake while the block was administered. However, based on the postoperative evaluation questions, the patients appeared to be unaware which block was performed. Finally, the use of drainage for psotoperative follow-up purposes during the surgical procedure was presumed to reduce the infiltration of bupivacaine into the surrounding tissue when administered as an IA injection.

In conclusion, the PENG block and QLB provided effective analgesia for up to 6 h postoperatively. The PENG block reduced opioid consumption during the first 6 h compared to IA local anesthetic injection. In addition, the motor-protective effect of the PENG block enabled earlier patient mobilization. However, similar results were obtained for the PENG block, QLB, and IA injection with respect to postoperative QoR.

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None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Tayfun Et (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)
Muhammet Korkusuz (Methodology; Writing – original draft; Writing – review & editing)

Supplementary Materials

Supplementary Material 1. Intragroup and intergroup comparisons of NRS static and dynamic values measured at 7 different time points.
Supplementary Table 1. Comparison of NRS scores measured at static in study groups.
Supplementary Table 2. Comparison of NRS scores measured at movement in study groups.

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Effects of dexmedetomidine on pulmonary function in patients receiving one-lung ventilation: a meta-analysis of randomized controlled trial

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Background: Mechanical ventilation, particularly one-lung ventilation (OLV), can cause pulmonary dysfunction. This meta-analysis assessed the effects of dexmedetomidine on the pulmonary function of patients receiving OLV.

Methods: The Embase, PubMed, MEDLINE, Cochrane Library, ClinicalTrials.gov, and Chinese Clinical Trial Registry databases were systematically searched. The primary outcome was oxygenation index (OI). Other outcomes including the incidence of postoperative complications were assessed.

Results: Fourteen randomized controlled trials involving 845 patients were included in this meta-analysis. Dexmedetomidine improved the OI at 30 (mean difference [MD]: 40.49, 95% CI [10.21, 70.78]), 60 (MD: 60.86, 95% CI [35.81, 85.92]), and 90 min (MD: 55, 95% CI [34.89, 75.11]) after OLV and after surgery (MD: 28.98, 95% CI [17.94, 40.0]) and improved lung compliance 90 min after OLV (MD: 3.62, 95% CI [1.7, 5.53]). Additionally, dexmedetomidine reduced the incidence of postoperative pulmonary complications (odds ratio: 0.44, 95% CI [0.24, 0.82]) and length of hospital stay (MD: −0.99, 95% CI [−1.25, −0.73]); decreased tumor necrosis factor-α, interleukin (IL)-6, IL-8, and malondialdehyde levels; and increased superoxide dismutase levels. However, only the results for the OI and IL-6 levels were confirmed by the sensitivity and trial sequential analyses.

Conclusions: Dexmedetomidine improves oxygenation in patients receiving OLV and may additionally decrease the incidence of postoperative pulmonary complications and shorten the length of hospital stay, which may be related to associated improvements in lung compliance, anti-inflammatory effects, and regulation of oxidative stress reactions. However, robust evidence is required to confirm these conclusions.

Keywords: Artificial respiration; Dexmedetomidine; Meta-analysis; One-lung ventilation; Postoperative complications; Respiratory mechanics.

Introduction

Mechanical ventilation, particularly one-lung ventilation (OLV), significantly reduces lung compliance and ventilation, which leads to pulmonary dysfunction ranging from temporary minor hypoxia to severe fatal manifestations (e.g., acute respiratory distress syndrome), especially in patients with pulmonary diseases [1,2]. Pulmonary dysfunction impairs patient outcomes and substantially increases the burden on the healthcare system regardless of its severity [3]. However, no protective modalities with consistent efficacy and safety are available at present [4]. Therefore, anesthesiologists continue to explore strategies to protect lung function.

Dexmedetomidine is a selective Alpha-2 agonist with various clinical uses in anesthesiology and intensive care [1]. Some studies have reported that in addition to its sedative and cardiovascular effects, dexmedetomidine also serves a protective function in respiratory mechanics and oxygenation both in animals [5–7] and in operative patients receiving mechanical ventilation [1,8,9]. However, another study showed that dexmedetomidine did not confer any protective effects on the lungs [10]. Therefore, this meta-analysis aimed to assess the effects of dexmedetomidine on pulmonary function in patients receiving OLV and provide reliable evidence for its clinical application.

Materials and Methods

This meta-analysis was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022352468). All modifications to the PROSPERO-registered protocol are described below.

Search strategy

The Embase, PubMed, Medline, Cochrane Library, ClinicalTrials.gov, and Chinese Clinical Trial Registry databases were comprehensively searched from their inception to October 21, 2022, by two reviewers (L.Y. and Y.C.) independently according to the search strategy (Supplementary Material 1), without restrictions on language or publication date. The search terms included the following: dexmedetomidine, respiratory, lung, pulmonary, breathing, respiration, oxygenation, PaO_2/FiO_2, P/F ratio, mechanics, compliance, dynamic compliance, Cdyn, resistance, peak inspiratory pressure, Ppeak, airway peak pressure, plateau pressure, dead space, transpulmonary pressure, intrapulmonary shunt, and Qs/Qt. Boolean logical operators were used to connect search terms. The references of identified trials and systematic reviews were also manually searched for additional potentially relevant trials.

Eligibility criteria

The inclusion criteria were as follows: (1) operative patients receiving OLV; (2) randomized controlled trials (RCTs), irrespective of language; (3) studies comparing the effects of intravenous dexmedetomidine infusion with placebo or blank infusion; and (4) studies with complete data on one of the following outcomes: PaO_2/FiO_2 or oxygenation index (OI), lung compliance, airway resistance, peak inspiratory pressure (Ppeak), plateau pressure (Pplat), dead space, transpulmonary pressure, and intrapulmonary shunt or Qs/Qt. Publications without full texts available or with unextractable data were excluded.

Data extraction

Two reviewers (L.Y. and Y.C.) independently used a standard data extraction form to retrieve relevant data. Discrepancies were identified and resolved through discussion with a third reviewer (B.C.) when necessary. The extracted data included details on the following: first author, country, study design, sample size, publication date, patient age and sex, interventions, type of surgery, inclusion and exclusion criteria, and outcomes.

The primary outcomes were the OI at 30, 60, and 90 min after OLV and after surgery. Secondary outcomes were lung compliance, airway resistance, Ppeak, Pplat, dead space ventilation, transpulmonary pressure, Qs/Qt, serum inflammatory factors, oxidative stress indices, mean arterial pressure (MAP), and heart rate (HR) at 30, 60, and 90 min after OLV and after surgery; postoperative pulmonary complications; and length of hospital stay.

Assessment of methodological quality

Two reviewers (L.Y. and Y.C.) independently assessed the quality of the RCTs based on the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions. A "risk of bias" table, which included details on the methods used for random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting, was created. Quantitative assessment of the quality of the RCTs was performed using a modified Jadad 7-point scale, where a Jadad score ≥ 4 indicates high-quality [12]. The overall quality of each study was evaluated as "low" or "high." Publication bias was assessed using a funnel plot when the number of included studies was ≥ 10 [13].

Statistical analysis

Review Manager software version 5.4 (Cochrane Collaboration, England) was used for this meta-analysis. The incidence of pulmonary complications was a dichotomous outcome, while the remaining outcomes were continuous. Odds ratios (ORs) and 95% CIs were used to assess dichotomous outcomes, while mean differences (MDs) and 95% CIs were used to assess continuous outcomes. The length of hospital stay and other continuous outcomes were assessed based on the difference between the value at the ob-

servational time point and the value before drug treatment. A meta-analysis was performed when an outcome was reported in two or more studies. Statistical heterogeneity among the included studies was assessed using P and I^2. A fixed-effects model was applied when $I^2 < 50\%$ and $P > 0.1$; otherwise a random-effects model was used. The inverse variance and Mantel-Haenszel methods were used to combine separate statistics. Statistical significance was set at $P < 0.05$. A sensitivity analysis was conducted by omitting one study in turn.

Trial sequential analysis (TSA) software version 0.9.5.10 (Copenhagen Trial Unit, Denmark) was used to examine the reliability and conclusiveness of the available evidence according to a previous meta-analysis [14,15]. A sufficient level of evidence was determined to have been reached for the anticipated intervention effect when the cumulative Z-curve crossed the TSA boundary and no further studies were needed. In contrast, when the Z-curve failed to cross the TSA boundary and the required information size (RIS) was not reached, the evidence was considered insufficient to reach a conclusion. Two-sided tests with a type I error of 5%, power of 80%, and low bias-based relative risk reduction were used to calculate the RIS.

Results

Search results

A total of 948 studies were identified, of which 929 were excluded after screening the titles and abstracts (Fig. 1). After screening the full text of the remaining 19 articles, one study published in 2017 [16] was excluded because it was extremely similar to another study published in 2016 [17]. Two studies by Xia et al. [18,19] reached the same conclusion; therefore, we only included the latest study [19]. Among the remaining 17 studies, three were excluded for the following reasons: one was not an RCT [20], one had no full text available [21], and one assessed the effect of nebulized dexmedetomidine [22]. Thus, 14 RCTs [1,8,9,17,19,23–31], with 845 total patients, were included in this meta-analysis.

The basic characteristics and interventions are summarized in Supplementary Table 1. All RCTs were published after 2010. One RCT [28] was published in the USA, whereas all remaining RCTs were published in Asia. In one RCT [24], dexmedetomidine was intravenously infused at a rate of 0.3 μg/kg/h, whereas, in the remaining RCTs, it was infused as a bolus dose of 0.3–1.0 μg/kg over 10 min and then as a continuous infusion at 0.3–0.5

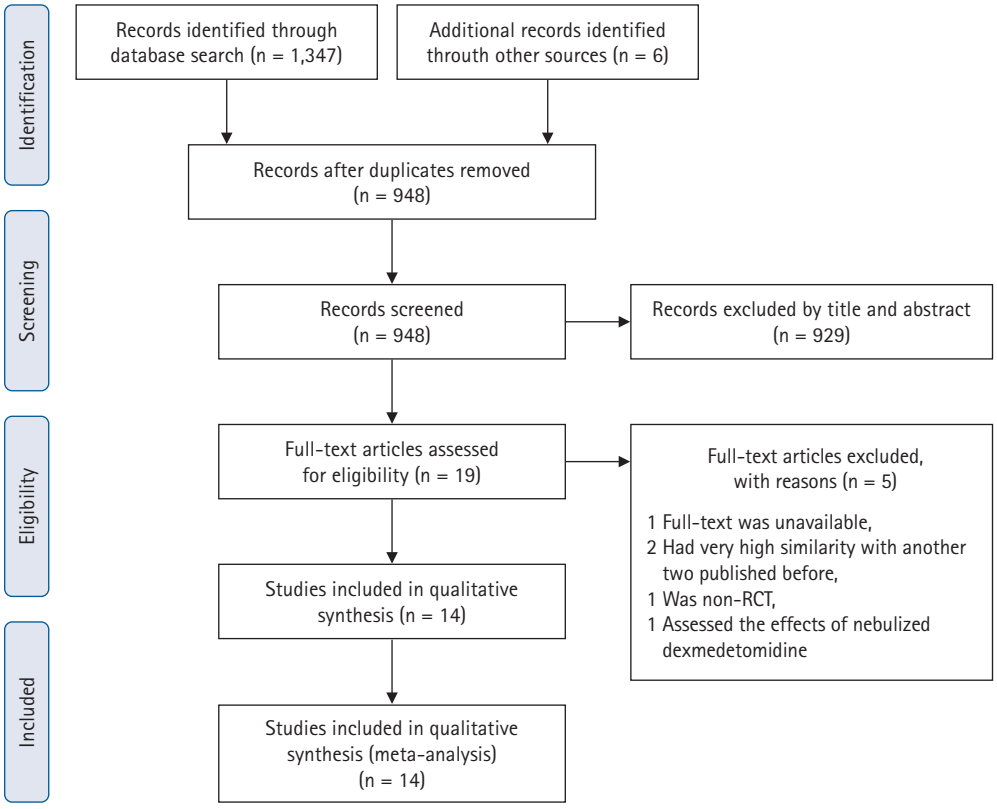

Fig. 1. "PRISMA" flow diagram.

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μg/kg/h. Two RCTs [1,25] investigated different doses of dexmedetomidine.

Risk of bias assessment

The quality of the RCTs was assessed using the risk of bias and modified Jadad scores (Table 1). Five RCTs [1,9,19,25,31] did not provide details regarding randomization. Five RCTs [8,17,19,25,28] reported the implementation of allocation concealment using sealed envelopes. Seven RCTs [8,9,17,19,25,27,28] reported the use of patient and participant blinding. None of the studies reported blinding of the outcome assessment. Eight RCTs [1,24,26–31] did not report the number and reasons for patient withdrawal or loss to follow-up; therefore, we determined that these studies had incomplete outcome data. The PaO_2 results in one RCT [1] were inconsistent with the data shown in the table; therefore, we concluded that the study selectively reported the outcomes. None of the other sources of bias were applicable. Eight RCTs [8,9,17,19,23,25,27,28] with a modified Jadad score ≥ 4 were rated as high quality.

Meta-analysis results

Oxygenation index

Five [24,26,28,29,31], three [17,26,29], three [17,24,29], and five [17,23,24,26,31] RCTs reported the OI at 30, 60, and 90 min after OLV and after surgery, respectively. Although the OI decreased in both the control and dexmedetomidine groups after OLV (Fig. 2), dexmedetomidine significantly improved the OI at 30 min (MD: 40.49, 95% CI [10.21, 70.78], P = 0.009), 60 min (MD: 60.86, 95% CI [35.81, 85.92], P < 0.001), and 90 min (MD: 55, 95% CI [34.89, 75.11], P < 0.001) after OLV and after surgery (MD: 28.98, 95% CI [17.94, 40.02], P < 0.001) compared with the control group.

Respiratory mechanics

The following indices were used to assess respiratory mechanics: lung compliance, Pplat, Ppeak, airway resistance, dead space ventilation, transpulmonary pressure, and Qs/Qt. However, only lung compliance, Pplat, and Qs/Qt were included in the meta-analysis. Two [1,24] and two [17,24] RCTs reported lung compliance at 30 and 90 min after OLV, respectively. Although dexmedetomidine did not improve lung compliance 30 min after OLV (MD: 12.22, 95% CI [−2.82, 27.26], P = 0.11), compliance improved significantly 90 min after OLV (MD: 3.62, 95% CI [1.7, 5.53], P < 0.001) compared with the control group (Fig. 3). Two RCTs [1,26] reported Pplat and three studies [1,19,25] reported Qs/Qt 30 min after OLV. The meta-analysis also showed that dexmedetomidine did not decrease the Pplat (MD: −10.41, 95% CI [−25.56, 4.73], P = 0.18; Supplementary Fig. 1) or Qs/Qt (MD: −7.45, 95% CI [−24.88, 9.79], P = 0.40; Supplementary Fig. 2) 30 min after OLV compared with the control group.

Table 1. Quality Assessment of the RCTs based on the Guidelines Provided in the Cochrane Handbook for Systematic Reviews of Interventions and the Modified Jadad 7-point Scale

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	No selective outcome reporting	Other source of bias	Jadad score	Quality
Asri 2020 [9]	?	?	√	–	√	√	√	5	High
Cui 2020 [23]	√	?	–	–	√	√	√	4	High
Gong 2020 [24]	√	?	–	–	–	√	√	3	Low
Gu 2017 [25]	?	√	√	–	√	√	√	6	High
Guo 2017 [26]	√	?	–	–	–	√	√	3	Low
Jannu 2020 [27]	√	?	√	–	–	√	√	5	High
Jiang 2022 [1]	?	?	–	–	–	–	√	2	Low
Kernan 2011 [28]	√	√	√	–	–	√	√	6	High
Lai 2013 [29]	√	?	–	–	–	√	√	3	Low
Lee 2016 [17]	√	√	√	–	√	√	√	7	High
Liu 2020 [30]	√	?	–	–	–	√	√	3	Low
Meng 2020 [31]	?	?	–	–	–	√	√	2	Low
Xia 2015 [19]	?	√	√	–	√	√	√	6	High
Zhu 2020 [8]	√	√	√	–	√	√	√	7	High

√: low risk of bias, ?: unclear risk of bias, –: high risk of bias. RCT: randomized controlled trial.

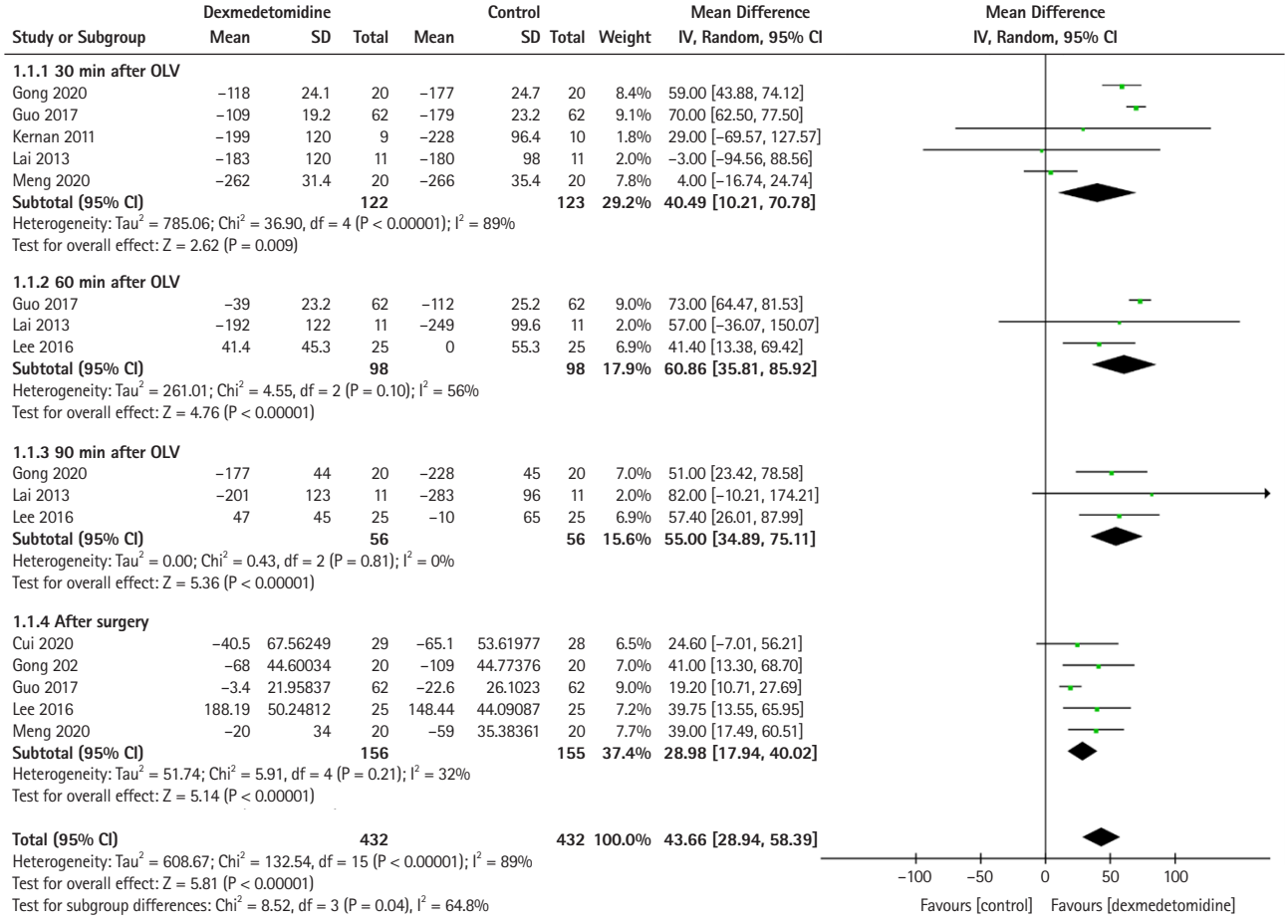

Fig. 2. Forest plot diagram showing the oxygenation index. SD: standard deviation, IV: inverse variance, OLV: one-lung ventilation.

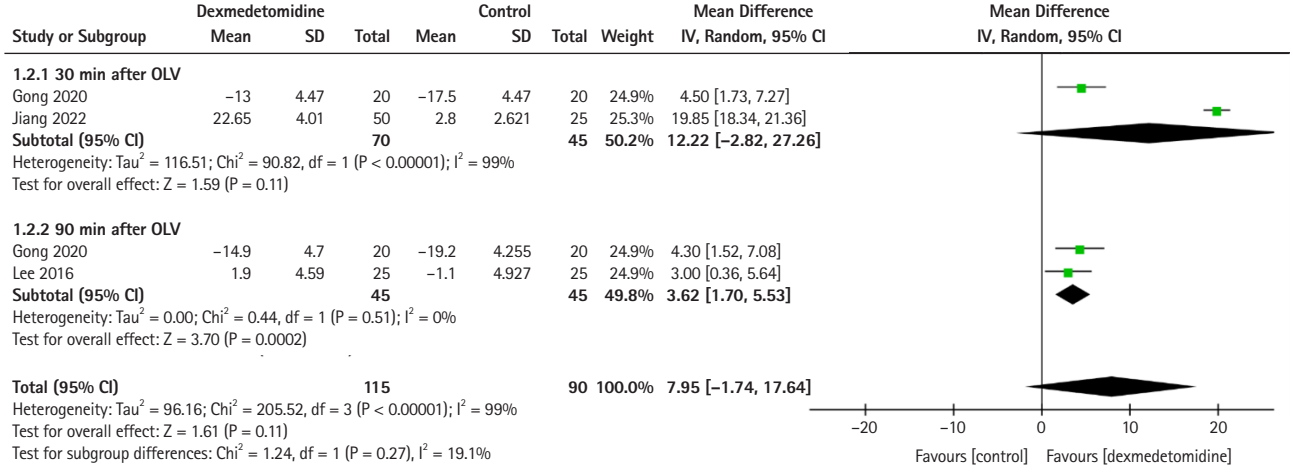

Fig. 3. Forest plot diagram showing lung compliance. SD: standard deviation, IV: inverse variance, OLV: one-lung ventilation.

Serum inflammatory factors

Tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8 were integrated to evaluate the effects of dexmedetomidine on inflammatory reactions. Three [1,8,26], two [26,30], and four [8,23,26,30] RCTs reported the TNF-α levels at 30 min after OLV, 60 min after OLV, and after surgery, respectively. This meta-anal-

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ysis showed that dexmedetomidine decreased the TNF-α levels significantly 30 min after OLV (MD: −20.38, 95% CI [−34.84, −5.92], P = 0.006) and after surgery (MD: −19.67, 95% CI [−34.51, −4.83], P = 0.009), but not 60 min after OLV (MD: −25.31, 95% CI [−54.48, 3.85], P = 0.09) compared with the control group (Supplementary Fig. 3). Three [1,8,24] and four [8,23,24,30] RCTs reported the level of IL-6 30 min after OLV and after surgery, respectively. Although the IL-6 levels were not significantly decreased 30 min after OLV (MD: −13.62, 95% CI [−34.48, 7.23], P = 0.2), they were significantly decreased after surgery (MD: −5.52, 95% CI [−8.00, −3.04], P < 0.001) in the dexmedetomidine group compared with the control group (Supplementary Fig. 4). Two RCTs [1,31] reported IL-8 levels 30 min after OLV. This meta-analysis found that dexmedetomidine significantly decreased the level of IL-8 30 min after OLV (MD: −37.57, 95% CI [−41.91, −33.24], P < 0.001; Supplementary Fig. 5) compared with the control group.

Serum oxidative stress indices

Malondialdehyde (MDA) and superoxide dismutase (SOD) were integrated to evaluate the effects of dexmedetomidine on oxidative stress reactions. Four [1,19,24,26], two [26,30], and three [24,26,30] RCTs reported MDA levels 30 min after OLV, 60 min after OLV, and after surgery, respectively. This meta-analysis found that dexmedetomidine greatly decreased the MDA levels at 30 min (MD: −3.47, 95% CI [−5.17, −1.78], P < 0.001) and 60 min (MD: −0.45, 95% CI [−0.81, −0.08], P = 0.02) after OLV and after surgery (MD: −0.58, 95% CI [−0.98, −0.17], P = 0.006) compared with the control group (Supplementary Fig. 6). Three [1,19,24] and two [24,30] RCTs reported MDA levels at 30 min after OLV and after surgery, respectively. Although SOD levels were not significantly increased 30 min after OLV (MD: 8.34, 95% CI [−3.62, 20.3], P = 0.17), they were significantly increased after surgery (MD: 29.07, 95% CI [22.01, 36.13], P < 0.001) in the dexmedetomidine group compared with the control group (Supplementary Fig. 7).

Hemodynamic indices

HR and MAP were integrated to evaluate the effects of dexmedetomidine on hemodynamic indices. Six RCTs [1,9,19,25,28,31] reported the HR and MAP values 30 min after OLV, and three RCTs [9,17,25] reported the HR and MAP values 60 min after OLV. This meta-analysis showed that dexmedetomidine did not significantly decrease HR at 30 min (MD: −2.13, 95% CI [−4.30, 0.04], P = 0.05) or 60 min (MD: −10.09, 95% CI [−20.48, 0.30], P = 0.06) after OLV compared with the control group (Supplementary Fig. 8). Additionally, dexmedetomidine did not significantly decrease MAP at 30 min (MD: −1.89, 95% CI [−3.81, 0.04], P = 0.05) or 60 min (MD: −10.25, 95% CI [−22.01, 1.51], P = 0.09) after OLV compared with the control group (Supplementary Fig. 9).

Postoperative pulmonary complications

Five RCTs [8,17,23,27,31] reported the incidence of postoperative pulmonary complications, including pulmonary infection, atelectasis, pneumonia, acute respiratory distress syndrome, purulent sputum, prolonged air leakage, and pulmonary embolism. This meta-analysis showed that dexmedetomidine significantly decreased the incidence of postoperative pulmonary complications (OR: 0.44, 95% CI [0.24, 0.82], P = 0.009; Fig. 4) compared with the control group.

Length of hospital stay

Four RCTs [8,17,27,31] reported the length of hospital stay. This meta-analysis showed that dexmedetomidine significantly decreased the length of hospital stay (MD: −0.99, 95% CI [−1.25, −0.73], P < 0.001; Fig. 5) compared with the control group.

Sensitivity analysis

The sensitivity analysis revealed that significant differences in the OI at 60 and 90 min after OLV and after surgery, IL-6 levels after surgery, and length of hospital stay between the dexmedetomidine and control groups persisted when one study was omitted in turn (Supplementary Table 2). The other outcome variables either showed no differences or sensitivity analyses could not be performed as only two RCTs were included.

TSA

The TSA showed that the Z-curves of the OI (Supplementary Fig. 10) and IL-6 levels (Supplementary Fig. 11) after surgery crossed the conventional and TSA boundaries, and the Z-curve of the length of hospital stay (Supplementary Fig. 12) crossed the conventional boundary but did not cross the TSA boundary.

Discussion

As this study aimed to assess the effects of dexmedetomidine on pulmonary function in operative patients receiving mechanical ventilation, the primary protocol of this meta-analysis was intended to include different types of surgery. However, after comprehensively searching the databases, we found several related studies that included patients undergoing OLV. To reduce bias, we adjusted the inclusion criteria to only include patients who underwent

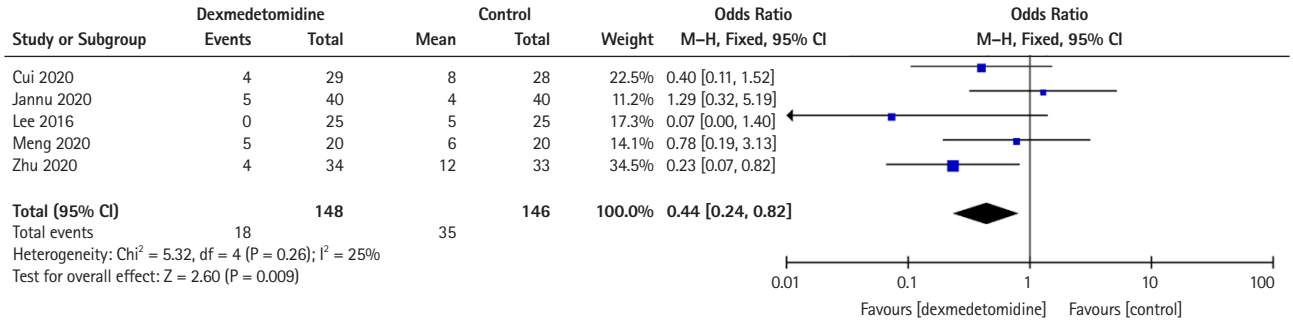

Fig. 4. Forest plot diagram showing postoperative pulmonary complications. IV: inverse variance, OLV: one-lung ventilation.

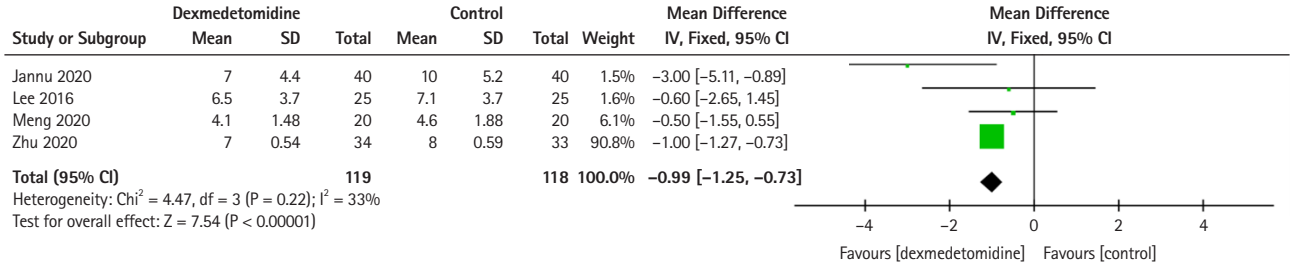

Fig. 5. Forest plot diagram showing the length of hospital stay. SD: standard deviation, IV: inverse variance, OLV: one-lung ventilation.

OLV. Our meta-analysis showed that dexmedetomidine infusion significantly improved the OI at 30, 60, and 90 min after OLV and after surgery. These results were confirmed using sensitivity analysis and TSA, and were consistent with two previous meta-analyses published by Bai et al. [2] and Huang et al. [32], which showed that intraoperative dexmedetomidine treatment improved oxygenation in patients receiving OLV. In addition, studies have reported that nebulized dexmedetomidine treatment improves PaO_2 during OLV [22] and intravenous dexmedetomidine treatment improves oxygenation both in morbidly obese patients undergoing bariatric surgery [33] and in patients with cervical cancer undergoing laparoscopy [34]. Taken together, these data strongly suggest that intraoperative dexmedetomidine treatment improves oxygenation in patients receiving mechanical ventilation.

Similar to the findings of the meta-analysis by Bai et al. [2], the current study also found that perioperative dexmedetomidine administration decreased the serum concentrations of TNF-α, IL-6, and IL-8 in patients receiving OLV. However, the anti-inflammatory effect of dexmedetomidine could not completely explain the increase in the OI at 30 min after OLV. As respiratory mechanics directly affect oxygenation, we evaluated the effects of dexmedetomidine on respiratory mechanics. This meta-analysis found that dexmedetomidine infusion significantly improved lung compliance 90 min after OLV. Although our study found that dexmedetomidine had no effect on lung compliance, Pplat, or intrapulmonary shunt 30 min after OLV, a limited number of RCTs were included. Moreover, although one meta-analysis [32] found that intraoperative dexmedetomidine treatment reduced the intrapulmonary shunt level during OLV, only five studies were included in the analysis, two of which were conducted by the same authors. Lee et al. [17] reported that intraoperative dexmedetomidine treatment decreased the Ppeak in patients with moderate chronic obstructive pulmonary disease undergoing lung cancer surgery. Jannu et al. [27] found that intraoperative dexmedetomidine treatment improved the forced expiratory volume in 1 s on postoperative days 1 and 2. Another retrospective study [35] found that intraoperative dexmedetomidine treatment reduced the Ppeak and airway resistance at the end of OLV. To the best of our knowledge, no previous meta-analysis has investigated the effects of dexmedetomidine on oxidative stress reactions. Our findings revealed that intraoperative dexmedetomidine treatment decreased serum MDA levels and increased serum SOD levels; however, the number of RCTs included was limited. Thus, although dexmedetomidine has the potential to improve respiratory mechanics and regulate oxidative stress, more high-quality RCTs are required to confirm these findings.

One concern of intraoperative dexmedetomidine treatment is cardiovascular side effects. However, our meta-analysis found no

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significant differences in HR or MAP between the dexmedetomidine and control groups. Similarly, one previous meta-analysis [36], which included 10 RCTs, showed that intraoperative dexmedetomidine infusion had little effect on MAP and HR during bariatric surgery. Although some meta-analyses [32,37] found that dexmedetomidine decreased the perioperative MAP and HR, others [38,39] found that perioperative dexmedetomidine infusions resulted in more stable hemodynamics. These results suggest that dexmedetomidine infusions are not associated with severe cardiovascular side effects.

Finally, we found that intraoperative dexmedetomidine treatment reduced the length of hospital stay and the incidence of postoperative pulmonary complications. Although the sensitivity analysis and TSA revealed these results to be inconclusive, they were highly consistent with those of other meta-analyses [36,40]. Based on the results, the mechanisms by which dexmedetomidine improves oxygenation and pulmonary function during OLV can be speculated. Dexmedetomidine inhibits lung inflammation, regulates oxidative stress, and improves lung compliance, leading to reduced alveolar edema, increased pulmonary gas exchange, and enhanced alveolar ventilation. Furthermore, improving oxygenation and pulmonary function decreases the incidence of postoperative pulmonary complications and the length of hospital stay. Considering the numerous advantages of dexmedetomidine and the lack of severe cardiovascular side effects, we recommend that dexmedetomidine be routinely used in patients receiving mechanical ventilation.

This meta-analysis had some limitations. First, except for the OI and IL-6 levels, we were unable to draw definitive conclusions regarding the remaining outcomes as the sample sizes were small and some studies were poorly designed. Second, the different starting times and doses of dexmedetomidine may have affected the results. Lastly, several of the included studies were performed in Asia, especially in China, and thus geographical limitations are present. As we know, authors in the same region may has more opportunities to communicate, thus, their results may be affected by each other. Moreover, it is unclear whether the results of this meta-analysis are suitable for patients in other regions, such as Europe and Africa.

Overall, intraoperative dexmedetomidine treatment improves oxygenation in patients receiving OLV and may decrease the incidence of postoperative pulmonary complications and shorten the length of hospital stay, which may be related to associated improvements in lung compliance, anti-inflammatory effects, and regulation of oxidative stress reactions. However, robust evidence is required to confirm these conclusions.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Author Contributions

Lin Yang (Data curation; Formal analysis; Investigation; Software; Writing – original draft)
Yongheng Cai (Data curation; Formal analysis; Investigation; Software; Writing – original draft)
Lin Dan (Supervision; Validation; Visualization; Writing – review & editing)
He Huang (Supervision; Validation; Visualization; Writing – review & editing)
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Supplementary Materials

Supplementary Material 1. Search strategy.
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Supplementary Fig. 12. Sequential trial analysis of length of hospital stay. RIS: required information size.

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Comparison of different nonsteroidal anti-inflammatory drugs for cesarean section: a systematic review and network meta-analysis

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Background: Cesarean section is associated with moderate to severe pain and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly employed. The optimal NSAID, however, has not been elucidated. In this network meta-analysis and systematic review, we compared the influence of control and individual NSAIDs on the indices of analgesia, side effects, and quality of recovery.

Methods: CDSR, CINAHL, CRCT, Embase, LILACS, PubMed, and Web of Science were searched for randomized controlled trials comparing a specific NSAID to either control or another NSAID in elective or emergency cesarean section under general or neuraxial anesthesia. Network plots and league tables were constructed, and the quality of evidence was evaluated with Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis.

Results: We included 47 trials. Cumulative intravenous morphine equivalent consumption at 24 h, the primary outcome, was examined in 1,228 patients and 18 trials, and control was found to be inferior to diclofenac, indomethacin, ketorolac, and tenoxicam (very low quality evidence owing to serious limitations, imprecision, and publication bias). Indomethacin was superior to celecoxib for pain score at rest at 8–12 h and celecoxib + parecoxib, diclofenac, and ketorolac for pain score on movement at 48 h. In regard to the need for and time to rescue analgesia COX-2 inhibitors such as celecoxib were inferior to other NSAIDs.

Conclusions: Our review suggests the presence of minimal differences among the NSAIDs studied. Nonselective NSAIDs may be more effective than selective NSAIDs, and some NSAIDs such as indomethacin might be preferable to other NSAIDs.

Keywords: Analgesia; Cesarean section; Non-steroidal anti-inflammatory agents; Obstetrical anesthesia; Postoperative pain; Systematic review.

Introduction

Cesarean section is one of the most common operations performed worldwide. It is, however, associated with moderate to severe pain in almost four fifths of women [1] and, when compared to many other surgical procedures, it has been reported to be the ninth most painful operation on the first postoperative day [2]. Pain during and following ce-

sarean section has been demonstrated to be of greatest concern to women [3], and inadequate pain relief has been related to negative effects on breastfeeding and infant care [1], maternal dissatisfaction [4], postpartum depression [5], and chronic pain [5,6].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used as part of a multimodal strategy in the perioperative period, and provide analgesia by the inhibition of cyclooxygenase enzymes that are involved in the formation of hyperalgesic prostaglandins [7]. In a meta-analysis that compared control to NSAIDs, NSAIDs decreased the pain score at rest at 12 h and 24 h and on movement at 24 h, lowered opioid consumption, and reduced the risk of sedation, the latter a recognized side effect of opioids [8]. Given this, the procedure specific postoperative pain management (PROSPECT) recommendations for elective cesarean section include the intraoperative use of intravenous NSAIDs and postoperative use of oral or intravenous NSAIDs [9]. It is still not clear, however, which NSAID is most effective in the setting of cesarean section. Different NSAIDs may produce varying pain relief efficacy and have differing side effect profiles, and hence a comparative analysis of NSAIDs is important. Several randomized trials investigating NSAIDs have been published recently [10,11], and a contemporary review would update the available evidence for the use of NSAIDs in cesarean section.

Our aim in this network meta-analysis and systematic review was to compare the influence of control and individual NSAIDs such as diclofenac and ibuprofen on the indices of analgesia, side effects, and quality of recovery. We hypothesized that we would establish the overall efficacy of NSAIDs in cesarean section, and potentially uncover differences among the NSAIDs studied.

Materials and Methods

We prospectively registered the protocol for the systematic review and network meta-analysis with PROSPERO (CRD42021264209), and our findings have been presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12]. The following databases, CDSR, CINAHL, CRCT, Embase, LILACS, PubMed, and Web of Science, were searched from inception to May 27, 2021, for free text keywords and subject headings associated with different permutations of terms related to cesarean section, obstetric analgesia, NSAIDs in general, and specific NSAID drug names (Supplementary Material 1).

Once duplicate citations were discarded, two authors (IM and ND) independently screened the titles and abstracts of the remaining citations against the inclusion and exclusion criteria in Rayyan (Qatar Computing Research Institute, 2016, Doha, Qatar) [13]. Inclusion criteria were defined as randomized controlled trials that compared a specific NSAID to either control or another NSAID in the context of elective or emergency cesarean section under general or neuraxial anesthesia. The timing of NSAID administration could be preoperative, intraoperative, and/or postoperative, and trials that investigated more than one NSAID, either combined or in more than one arm, were included. Exclusion criteria included trials in which regional anesthesia or wound catheters were utilized postoperatively. Trials that included intraoperative local anesthetic infiltration and single-shot transversus abdominis plane block, for example, were included, but those that used postoperative infusions of local anesthetic through catheters into the epidural space, transverse abdominis plane, or wound were excluded. No limits were placed on the language of publication. Cases of disagreement were resolved by a third author (BC). If a trial was thought to be eligible for inclusion, then we carried out a full text review to confirm this. In order to seek further trials not identified by our search strategy, one author (AC) searched the reference lists of included trials and previously published systematic reviews.

Data extraction was conducted and checked by five authors (IM, AC, PS, JO, and ND). The following characteristics of trials were extracted: number of patients in each group; nature of cesarean section; mode of anesthesia; intraoperative regional anesthesia and systemic analgesia; dose, route, and timing of NSAID administration; regular postoperative analgesia; and management of postoperative breakthrough pain. The primary outcome was the cumulative intravenous morphine equivalent consumption at 24 h, and the MCID was prespecified at 10 mg. It is the opinion of the authors that this outcome is particularly important as it provides a measure of pain and need for rescue analgesia on the first postoperative day, and increased opioid consumption has been associated with side effects such as nausea and vomiting, urinary retention, constipation, and sleep disturbance that can lead to distress and interfere with postoperative recovery [14]. In a systematic review, the clinician perceived the MCID estimate for this primary outcome in the setting of total hip and knee arthroplasty was 10 mg and, in the absence of evidence-based and patient-rated MCIDs, we concurred with this [15]. Secondary outcomes included: pain score at rest and on movement at 8–12 h, 24 h, and 48 h; need for rescue analgesia and time to first analgesic request; cumulative intravenous morphine consumption at 8–12 h, 48 h, and in-hospital; incidence of postoperative nausea and/or vomiting, pruritus, and sedation at 24 h, 48 h, and in-hospital; quality of recovery-15 (QoR-15) [16] at 24 h and 48 h; and hospital length of stay. No other secondary outcomes were considered. We extracted dichotomous data as numbers and continuous data as

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means and standard deviations. If data were presented as medians, these were assumed to be equal to the means, and the standard deviations were calculated by dividing the interquartile range by 1.35 or the range by 4 as per guidance from the Cochrane Collaboration [17]. In cases where data were presented only in graphical format, PlotDigitizer™ (Version 2.1, Free Software Foundation, USA) was utilized in order to facilitate numerical extraction. Opioid conversion was performed with reference to the British National Formulary [18] and Faculty of Pain Medicine [19]. Where the data were not published or unclear, the authors were emailed up to three times for clarification.

Subsequent to data extraction, the data were transferred from Microsoft Excel® (Microsoft, USA) into Stata (Version 16.1, StataCorp LLC, USA) by one author (ND) and then checked by a second author (IM). We conducted this network meta-analysis with a frequentist method on any outcome of interest if three or more competing interventions could be connected into a network through direct comparisons between the trials [20,21]. Network plots were produced for all outcomes subjected to network meta-analysis with a common heterogeneity parameter and multivariate methods. In these network plots, the nodes depicted the interventions and the connecting lines represented the direct comparisons between the interventions. If interventions were not directly compared within trials, indirect comparisons via a common comparator were mathematically derived using results from the various direct intervention effects. Consistency was locally and globally assessed between direct and indirect estimates by the Separating Indirect from Direct Evidence technique and with the design-by-treatment interaction test, respectively. The results of comparisons between the different interventions were presented in network league tables as mean differences and 95% CIs for continuous outcomes and odds ratios and 95% CIs for dichotomous outcomes. If serious imprecision was not present for a particular outcome, competing interventions were ranked in order. We performed pairwise meta-analysis in Review Manager® (Version 5.3, The Nordic Cochrane Centre, Denmark) for those outcomes that were not analyzable by network meta-analysis but were reported by two or more randomized controlled trials. Heterogeneity was calculated with predetermined thresholds for low (25%–49%), moderate (50%–74%), and high (≥ 75%) levels [22], and the fixed and random effects model used for low and moderate or high heterogeneity, respectively. Tests were two-tailed and statistical significance was represented at the 5% level. The results were presented as mean differences and 95% CIs for continuous outcomes and risk ratios and 95% CIs for dichotomous outcomes.

The quality of evidence for every outcome was evaluated by two authors (IM and ND) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [23] and with the CINeMA software® (Institute of Social and Preventative Medicine, University of Bern, Switzerland). Fundamental components of quality include: risk of bias, indirectness, imprecision, inconsistency, and publication bias. Risk of bias was determined by two authors (JO and DO) using the Cochrane Risk of Bias 2 (RoB 2) tool [24] to examine the following: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Cases of disagreements were resolved by a third author (ND). Publication bias was examined with a comparison-adjusted funnel plot and the Egger's linear regression test.

Results

In all, we included 47 trials in this review [10,11,25–69] and details of the screening process are illustrated in Fig. 1. The following interventions were compared: control vs. celecoxib in two trials [35,46]; control vs. celecoxib + parecoxib in one trial [57]; control vs. diclofenac in 24 trials [11,25–34,36–43,65–69]; control vs. diclofenac vs. indomethacin in one trial [44]; control vs. diclofenac vs. ketoprofen in one trial [45]; control vs. ibuprofen vs. ketorolac in one trial [47]; control vs. indomethacin in one trial [48]; control vs. ketorolac in six trials [10,49–53]; control vs. naproxen in one trial [54]; control vs. parecoxib in one trial [55]; control vs. tenoxicam in six trials [56,58–62]; diclofenac vs. ketoprofen in one trial [63]; and ketorolac vs. parecoxib in one trial [64]. The findings of the risk of bias assessment are presented in Fig. 2. Overall, only four trials were deemed to be at low risk of bias [10,54,55,68], and 30 and 13 of the remaining trials were evaluated to have some concerns [25,27–35,37,38,43–45,47,49,52,53,57–67] or be at high risk of bias [11,26,36,39–42,46,48,50,51,56,69], respectively. Many of the concerns were related to the randomization process, measurement of the outcome, and the selection of the reported result. Of the 21 authors we emailed to clarify on methodology or results, nine responded with the requested information [38,42,43,50,53,55,61,62,65].

Characteristics of the trials are presented in Table 1. In regard to the nature of the cesarean section, it was elective, elective or emergent, and not specified in 30 [10,26,29,31–35,37,38,45,48–51,53–58,60–62,64–69], six [11,30,40–43], and 11 [25,27,28,36,39,44,46,47,52,59,63] trials, respectively. The mode of anesthesia was spinal, combined spinal-epidural (CSE), epidural, or general anesthesia in 27 [10,11,29,32–35,37–39,41–44,46,48,50,54–56,60–64,68,69], two [51,57], three [49,66,67], and 11 [25–28,30,31,47,53,58,59,65] trials, respectively. Of the remaining trials, one performed spinal or epidural anesthesia [45], two used neuraxial or

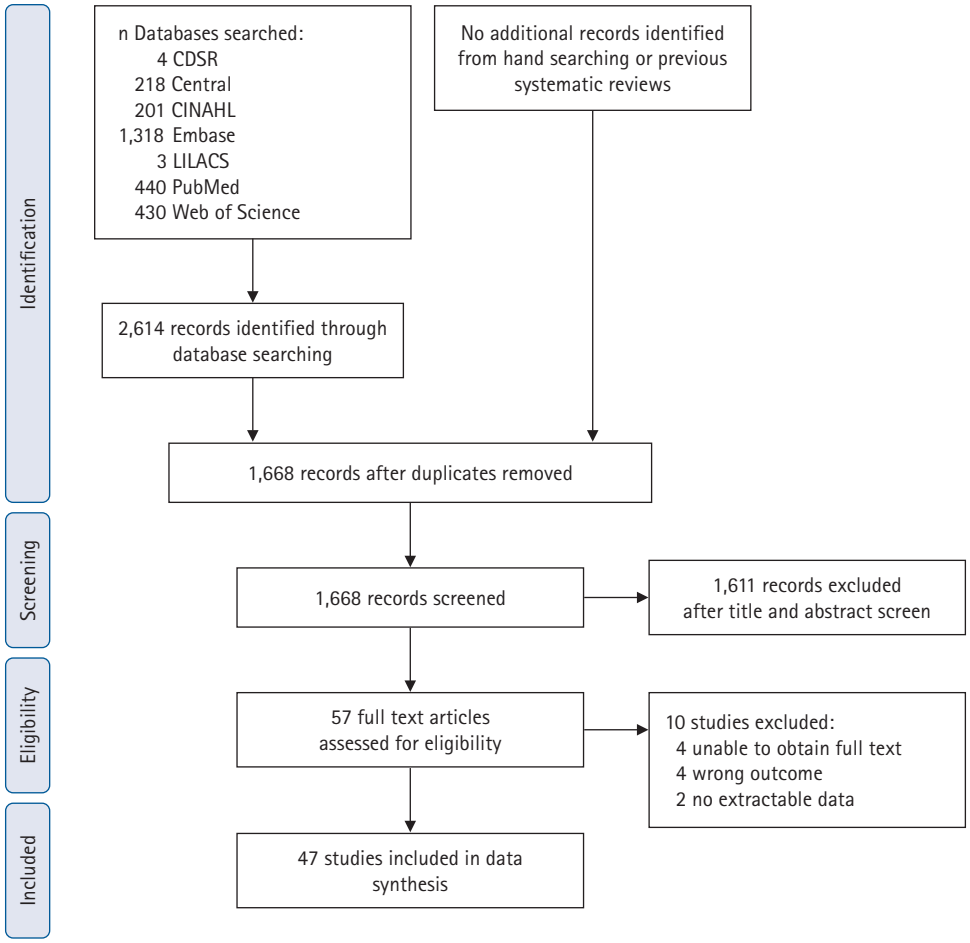

Fig. 1. PRISMA flow diagram summarizing the retrieved, included, and excluded randomized controlled trials. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

general anesthesia [40,52], and one did not specify the type of anesthesia [36]. Single-shot transversus abdominis plane block was utilized in one trial [11]. In addition to NSAIDs, women received propacetamol or paracetamol in four trials [32,33,37,57]. The route of administration of NSAIDs was as follows: oral in two trials [35,46]; intramuscular in 13 trials [25,27,28,31,34,36,38,40,43,49,65–67]; intravenous in 16 trials [10,11,39,45,50–53,55,56,58–62,64]; rectal in 11 trials [26,29,30,32,33,41,42,44,48,68,69]; oral or intramuscular in one trial [47]; intravenous and oral in one trial [57]; intramuscular or intravenous in one trial [63]; and rectal and oral in two trials [37,54]. In 21 trials, just one dose of NSAIDs was administered [10,11,26,35,36,39,46,49,55,56,58–63,65–69] and in further 21 trials, more than one dose or an infusion of NSAIDs was given [25,29–33,37,38,40,42–45,48,50–54,57,64]. Some trials provided NSAIDs only when the pain was reported to be at least moderate in intensity [34,41], or the pain score was greater than or equal to seven on a scale of zero to 10 [27,28] or higher than or equal to 60 on a scale of zero to 100 [47].

Our primary outcome, the cumulative intravenous morphine equivalent consumption at 24 h, was evaluated in 1,228 patients and 18 trials [27–29,32–34,37,39,44–46,50,52,55,58,61,62,64]. In the network plot, nine direct and 12 indirect comparisons were established between seven interventions (Fig. 3). With an MCID of 10 mg, control was clinically and statistically inferior to diclofenac, indomethacin, ketorolac, and tenoxicam (Table 2). No other statistical differences were demonstrated between the various NSAIDs. Evidence for local or global inconsistency was not found and the standard deviation of between-trials heterogeneity was 11.08. Inspection of the comparison-adjusted funnel plot (Supplementary Fig. 1) and the results of Egger's test (P = 0.011) revealed the presence of publication bias. The quality of evidence was graded as very low (Supplementary Material 2), and the network ranking of interventions was not performed in view of the serious imprecision (Supplementary Material 3).

Details of the results of the secondary outcomes are presented

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Fig. 2. Risk of bias assessment of included trials using the revised Cochrane tool.

in Table 3 and Supplementary Material 3, and information related to their network plots, inconsistency plots, contribution plots, predictive interval plots, and comparison-adjusted funnel plots is provided in Supplementary Material 4. Differences between NSAIDs were shown for some of these outcomes. For the pain score at rest at 8–12 h, indomethacin was clinically and statistically superior to celecoxib, and for the pain score on movement at 48 h, indomethacin was clinically and statistically superior to celecoxib + parecoxib, diclofenac, and ketorolac. In regard to the need for rescue analgesia, ketoprofen was clinically and statistically superior to celecoxib + parecoxib, and with respect to the time for rescue analgesia, diclofenac, ibuprofen, indomethacin, and ketorolac were clinically and statistically superior to celecoxib. In terms of side effects, ketoprofen was clinically and statistically su-

Table 1. Characteristics of the Included Trials

Reference	Group (n)	Journal title	Language	Country of the enrolled patients	Nature of cesarean section	Mode of anesthesia	Intraoperative regional anesthesia and systemic analgesia	Dose, route, and timing of NSAID administration	Regular postoperative analgesia	Management of postoperative breakthrough pain
Control vs celecoxib										
Lee et al. 2004 [35]	Control (30) Celecoxib (30)	Anaesthesia	English	Hong Kong	Elective; Pfannensteil approach	Spinal	Spinal: 3 ml 0.5% hyperbaric bupivacaine with morphine 300 μg	P.O. celecoxib 200 mg, once only, following delivery of neonate	Not specified	P.O. paracetamol and dextropropoxyphene
Fong et al. 2008 [46]	Control (20) Celecoxib (40)	British Journal of Anaesthesia	English	Taiwan, Republic of China	Not specified	Spinal	Not specified	P.O. celecoxib 400 mg, once only, either 30 min before spinal anesthesia or following surgical wound closure	I.V. morphine PCA	Not specified
Control vs celecoxib and parecoxib										
Paech et al. 2014 [57]	Control (55) Celecoxib and parecoxib (56)	Anaesthesia and Intensive Care	English	Australia	Elective; Pfannensteil approach	CSE	CSE: 2.1–2.5 0.5% hyperbaric bupivacaine with fentanyl 15 μg Systemic: I.V. paracetamol 2 g in only some groups	I.V. parecoxib 40 mg following delivery of neonate and P.O. celecoxib 400 mg at 12 h	P.O. paracetamol 1 g at 6, 12, and 18 h in only some groups. Patient-controlled epidural analgesia with bolus of pethidine 20 mg and lockout interval of 15 min	P.O. tramadol
Control vs diclofenac										
Bush et al. 1992 [65]	Control (25) Diclofenac (23)	Anaesthesia	English	United Kingdom	Elective; Pfannensteil approach	General anesthesia	Systemic: I.V. papaveretum 0.3 mg/kg	I.M. diclofenac 75 mg, once only, prior to discontinuation of general anesthesia	I.V. papaveretum PCA	Opioid, otherwise not specified
Sun et al. 1992 [66]	Control (58) Diclofenac (59)	Anesthesia and Analgesia	English	Taiwan, Republic of China	Elective; surgical approach not specified	Epidural	Epidural: 2% lidocaine with adrenaline 5 μg/ml of unspecified volume, followed by morphine 2 mg in only some groups subsequent to delivery of placenta	I.M. diclofenac 75 mg, once only, on arrival to recovery	Not specified	I.M. pethidine
Sun et al. 1993 [67]	Control (20) Diclofenac (20)	Anesthesia and Analgesia	English	Taiwan, Republic of China	Elective; surgical approach not specified	Epidural	Epidural: 2% lidocaine with adrenaline 5 μg/ml of unspecified volume, followed by morphine 4 mg subsequent to delivery of placenta	I.M. diclofenac 75 mg, once only, on arrival to recovery	Not specified	I.M. pethidine
Luthman et al. 1994 [68]	Control (23) Diclofenac (27)	International Journal of Obstetric Anesthesia	English	United Kingdom	Elective; surgical approach not specified	Spinal	Spinal: 2.75 ml 0.5% hyperbaric bupivacaine	P.R. diclofenac 100 mg, once only, at the end of surgery	I.V. morphine PCA	Not specified

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Table 1. Continued

Reference	Group (n)	Journal title	Language	Country of the enrolled patients	Nature of cesarean section	Mode of anesthesia	Intraoperative regional anesthesia and systemic analgesia	Dose, route, and timing of NSAID administration	Regular postoperative analgesia	Management of postoperative breakthrough pain
Dennis et al. 1995 [69]	Control (25) Diclofenac (25)	Anaesthesia	English	United Kingdom	Elective; surgical approach not specified	Spinal	Spinal: 2.5 ml 0.5% hyperbaric bupivacaine with morphine 200 μg	P.R. diclofenac 100 mg, once only, at the end of surgery	Not specified	P.O. paracetamol and dextropropoxyphene, and I.M. or I.V. morphine
Lee et al. 1997 [25]	Control (90) Diclofenac (90)	Korean Journal of Anesthesiology	Korean	Korea	Not specified	General anesthesia	None	I.M. diclofenac 75 mg following incidence of postoperative pain and further doses every 12 h	I.V. pethidine or morphine PCA depending on group allocation	Not specified
Sia et al. 1997 [26]	Control (30) Diclofenac (30)	Singapore Medical Journal	English	Singapore	Elective; surgical approach not specified	General anesthesia	Systemic: I.V. morphine 10 mg	P.R. diclofenac 100 mg, once only, following induction of general anesthesia and prior to surgical incision	I.V. morphine at a rate of 1.5 mg/h	I.M. pethidine
Kim et al. 1999 [27]	Control (40) Diclofenac (40)	Korean Journal of Anesthesiology	Korean	Korea	Not specified	General anesthesia	None	I.M. diclofenac 75 mg following incidence of postoperative pain equal to or greater than 7 out of 10 and further doses every 12 h	I.V. pethidine or morphine PCA	Not specified
Lee et al. 1999 [28]	Control (30) Diclofenac (30)	Korean Journal of Obstetrics and Gynecology	Korean	Korea	Not specified	General anesthesia	None	I.M. diclofenac 75 mg following incidence of postoperative pain equal to or greater than 7 out of 10 and further doses every 12 h	I.V. pethidine PCA	Not specified
Olofsson et al. 2000 [29]	Control (25) Diclofenac (25)	European Journal of Obstetrics Gynecology and Reproductive Biology	English	Sweden	Elective; surgical approach not specified	Spinal	Spinal: 2.5 ml 0.5% hyperbaric bupivacaine	P.R. diclofenac 50 mg at the end of surgery and two further doses in the first 24 h	I.V. ketobemidone PCA	I.V. ketobemidone
Rashid et al. 2000 [30]	Control (20) Diclofenac (20)	Saudi Medical Journal	English	Saudi Arabia	Elective or emergent; surgical approach not specified	General anesthesia	Not specified	P.R. diclofenac 100 mg at the end of surgery, 50 mg at 12 h, and 100 mg at 36 h	Not specified	I.M. pethidine
Al-Waili et al. 2001 [31]	Control (60) Diclofenac (60)	Archives of Medical Research	English	United Arab Emirates	Elective Surgical approach not specified	General anesthesia	Not specified	I.M. diclofenac 75 mg following incidence of postoperative pain and up to every 12 h thereafter	Not specified	I.M. pethidine

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Table 1. Continued

Reference	Group (n)	Journal title	Language	Country of the enrolled patients	Nature of cesarean section	Mode of anesthesia	Intraoperative regional anesthesia and systemic analgesia	Dose, route, and timing of NSAID administration	Regular postoperative analgesia	Management of postoperative breakthrough pain
Siddik et al. 2001 [32]	Control (40) Diclofenac (39)	Regional Anesthesia and Pain Medicine	English	Lebanon	Elective; surgical approach not specified	Spinal	Spinal: 1.6 ml 0.75% hyperbaric bupivacaine with fentanyl 12.5 μg. Systemic: I.V. propacetamol in only some groups	P.R. diclofenac 100 mg at the time of skin closure and further doses every 8 h in the first 24 h	I.V. propacetamol 2 g every 8 h in the first 24 h in only some groups. I.V. morphine PCA	I.V. morphine
Dahl et al. 2002 [33]	Control (42) Diclofenac (40)	International Journal of Obstetric Anesthesia	English	Norway	Elective; surgical approach not specified	Spinal	Spinal: 2.2–2.4 ml 0.5% hyperbaric bupivacaine	P.R. diclofenac 100 mg on arrival to recovery, 12 h, and 24 h	P.O. paracetamol 1 g every 6 h	I.V. morphine
Wilder-Smith et al. 2003 [34]	Control (60) Diclofenac (60)	Anesthesia and Analgesia	English	South Africa	Elective; surgical approach not specified	Spinal	Spinal: 1.8–2 ml 0.5% hyperbaric bupivacaine	I.M. diclofenac 75 mg following regression of sensory blockade to T10 and pain severity reported to be moderate	I.M. tramadol 100 mg as stat only in only some groups	I.V. morphine
Bourlert et al. 2005 [36]	Control (30) Diclofenac (34)	Journal of the Medical Association of Thailand	English	Thailand	Not specified if elective or emergent; Pfannensteil approach	Not specified	Not specified	I.M. diclofenac 75 mg, once only, postoperatively	I.M. morphine 10 mg as stat dose. I.V. morphine PCA	Not specified
Munishankar et al. 2008 [37]	Control (24) Diclofenac (25)	Anaesthesia	English	United Kingdom	Elective; surgical approach not specified	Spinal	Spinal: 2.25–2.5 ml 0.5% hyperbaric bupivacaine with fentanyl 12.5 μg	P.R. diclofenac 100 mg at the end of surgery followed by P.O. diclofenac 50 mg every 8 h	P.R. paracetamol 1 g. P.O. paracetamol 1 g every 6 h. I.V. morphine PCA	I.V. morphine
Surakarn et al. 2009 [38]	Control (40) Diclofenac (40)	Journal of the Medical Association of Thailand	English	Thailand	Elective; low midline approach	Spinal	Spinal: hyperbaric bupivacaine 10–12 mg with morphine 200 μg	I.M. diclofenac 75 mg within 2 h of the end of surgery and at 12 h	Not specified	I.M. tramadol
Thiengthong et al. 2012 [39]	Control (15) Diclofenac (14)	Acta Anaesthesiologica Taiwanica	English	Thailand	Not specified if elective or emergent; Pfannensteil approach	Spinal	Spinal: 2.2–2.5 ml 0.5% hyperbaric bupivacaine with morphine 200 μg	I.V. diclofenac 75 mg, once only, at 12 h	None	I.V. tramadol
Adamou et al. 2014 [40]	Control (80) Diclofenac (80)	Nigerian Medical Journal	English	Nigeria	Elective or emergent; surgical approach not specified	Neuraxial or general anesthesia	Determined by anesthesiologist	I.M. diclofenac 1 mg/kg following the end of surgery and every 12 h for 48 h	I.M. pentazocine 1 mg/kg every 6 h for 48 h	Not specified
Lotfalizade et al. 2015 [41]	Control (33) Diclofenac (33)	Iranian Journal of Obstetrics, Gynecology and Infertility	Persian	Iran	Elective or emergent; surgical approach not specified	Spinal	Spinal: 2.4 ml 0.5% hyperbaric bupivacaine with adrenaline 200 μg and fentanyl 20 μg	P.R. diclofenac 100 mg of unspecified frequency following pain severity reported to be moderate	Tramadol 100 mg of unspecified route	Not specified

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Table 1. Continued

Reference	Group (n)	Journal title	Language	Country of the enrolled patients	Nature of cesarean section	Mode of anesthesia	Intraoperative regional anesthesia and systemic analgesia	Dose, route, and timing of NSAID administration	Regular postoperative analgesia	Management of postoperative breakthrough pain
Olateju et al. 2016 [42]	Control (52) Diclofenac (64)	Middle East Journal of Anesthesiology	English	Nigeria	Elective or emergent; low midline or Pfannensteil	Spinal	Spinal: 0.5% hyperbaric bupivacaine of unspecified volume	P.R. diclofenac 100 mg at the end of surgery, 12 h, and 24 h	I.M. pentazocine 30 mg every 6 h for 24 h	I.M. tramadol
Egede et al. 2017 [43]	Control (70) Diclofenac (70)	Journal of Clinical and Diagnostic Research	English	Nigeria	Elective or emergent; Pfannensteil approach	Spinal	Not specified	I.M. diclofenac 75 mg within 1 h of the end of surgery and every 12 h for 24 h	I.M. pentazocine 30 mg every 4 h for 24 h	I.M. pentazocine
Kanta et al. 2021 [11]	Control (30) Diclofenac (30)	Indian Journal of Anaesthesia	English	India	Elective or emergent; surgical approach not specified	Spinal	Spinal: 2.5 ml 0.5% hyperbaric bupivacaine with morphine 200 μg. TAP block: 1.5 mg/kg 0.75% ropivacaine on each side	I.V. diclofenac 75 mg following delivery of neonate	Not specified	I.M. diclofenac
Control vs diclofenac vs indomethacin										
Akhavanakbari et al. 2013 [44]	Control (30) Diclofenac (30) Indomethacin (30)	Perspectives in Clinical Research	English	Iran	Not specified if elective or emergent; surgical approach not specified	Spinal	Spinal: 1.5–2 ml hyperbaric 5% lidocaine	P.R. diclofenac 50 mg or indomethacin 50 mg at the end of surgery and every 6 h for 24 h	Not specified	I.M. pethidine
Control vs diclofenac vs ketoprofen										
Rorarius et al. 1993 [45]	Control (30) Diclofenac (29) Ketoprofen (30)	British Journal of Anaesthesia	English	Finland	Elective; surgical approach not specified	Spinal or epidural	Spinal: 2.5–2.8 ml 0.5% hyperbaric bupivacaine. Epidural: Up to 20 ml 0.5% bupivacaine with or without 1% prilocaine if needed	I.V. diclofenac 150 mg or ketorolac 200 mg started at the end of surgery as an infusion over 24 h	Not specified	I.M. oxycodone
Control vs ibuprofen vs ketorolac										
Pagnoni et al. 1996 [47]	Control (32) Ibuprofen (30) Ketorolac (30)	Clinical Drug Investigation	English	Italy	Not specified	General anesthesia	Systemic: I.V. fentanyl 0.1 μg/kg	I.M. ketorolac 30 mg or P.O. ibuprofen, once only, following incidence of postoperative pain equal to or greater than 60 out of 100	Not specified	I.M. ketoprofen
Control vs indomethacin										
Pavy et al. 1995 [48]	Control (15) Indomethacin (15)	Anaesthesia and Intensive Care	English	Australia	Elective; Pfannensteil approach	Spinal	Spinal: 1.2–1.4 ml 0.75% hyperbaric bupivacaine with fentanyl 10–15 μg and morphine 250–300 μg	P.R. indomethacin 200 mg at the end of surgery followed by P.R. indomethacin 100 mg every 12 h for 72 h	None	P.O. paracetamol and codeine, and parenteral opioids

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Table 1. Continued

Reference	Group (n)	Journal title	Language	Country of the enrolled patients	Nature of cesarean section	Mode of anesthesia	Intraoperative regional anesthesia and systemic analgesia	Dose, route, and timing of NSAID administration	Regular postoperative analgesia	Management of postoperative breakthrough pain
Control vs ketorolac										
Tzeng et al. 1994 [49]	Control (30) Ketorolac (30)	Annals of the Academy of Medicine, Singapore	English	Taiwan, Republic of China	Elective; surgical approach not specified	Epidural	Epidural: 2% lidocaine with adrenaline 5 μg/ml of unspecified volume, followed by morphine 2 mg postoperatively	I.M. ketorolac 30 mg, once only, following incidence of postoperative pain	Not specified	I.M. pethidine
Cohen et al. 1996 [50]	Control (12) Ketorolac (13)	International Journal of Obstetric Anesthesia	English	United States of America	Elective; Pfannensteil approach	Spinal	Spinal: 1.6 ml 0.75% hyperbaric bupivacaine and morphine 100 μg Systemic: I.V. fentanyl 50–100 μg if needed	I.V. ketorolac 60 mg 1 h after spinal anesthesia followed by I.V. ketorolac 30 mg every 6 h for three doses	Not specified	I.V. pethidine
Pavy et al. 2001 [51]	Control (20) Ketorolac (24)	Anesthesia and Analgesia	English	Australia	Elective; surgical approach not specified	CSE	CSE: 2–2.5 0.5% hyperbaric bupivacaine with fentanyl 12.5 μg	I.V. ketorolac 15–30 mg after delivery of neonate followed by I.V. ketorolac 105–120 mg started in recovery as an infusion over 24 h	Patient-controlled epidural analgesia with bolus of pethidine 24 mg and lockout interval of 15 min	P.O. paracetamol and codeine
Lowder et al. 2003 [52]	Control (22) Ketorolac (22)	American Journal of Obstetrics and Gynecology	English	United States of America	Not specified if elective or emergent; Pfannensteil approach	Neuraxial or general anesthesia	Determined by anesthesiologist	I.V. ketorolac 30 mg at the end of surgery and two further doses at unspecified time interval	I.V. hydromorphone, pethidine, or morphine PCA	Not specified
El-Tahan et al. 2007 [53]	Control (45) Ketorolac (45)	International Journal of Obstetric Anesthesia	English	Egypt	Elective; Pfannensteil approach	General anesthesia	Systemic: I.V. fentanyl 1 μg/kg	I.V. ketorolac 15 mg before induction of general anesthesia followed by I.V. ketorolac as an infusion of 7.5 mg/hr until the end of surgery	None	I.V. tramadol
Khezri et al. 2018 [10]	Control (50) Ketorolac (50)	Caspian Journal of Internal Medicine	English	Iran	Elective; surgical approach not specified	Spinal	Spinal: 2.5 ml 0.5% bupivacaine of unspecified baricity	I.V. ketorolac 30 mg, once only, before spinal anesthesia	Not specified	I.V. paracetamol
Control vs naproxen										
Angle et al. 2002 [54]	Control (40) Naproxen (40)	Anesthesia and Analgesia	English	Canada	Elective Pfannensteil approach	Spinal	Spinal: 1.2–1.8 ml 0.75% hyperbaric bupivacaine with fentanyl 10–20 μg and morphine 200 μg	P.R. naproxen 500 mg 1 h at the end of surgery followed by P.O. naproxen 550 mg every 12 h for 72 h	Not specified	P.O. paracetamol and codeine, and I.M. pethidine or morphine
Control vs parecoxib										
Inthigood et al. 2017 [55]	Control (41) Parecoxib (41)	Journal of Obstetrics and Gynaecology Research	English	Thailand	Elective; low midline or Pfannensteil approach	Spinal	Spinal: 2 ml 0.5% hyperbaric bupivacaine with morphine 200 μg	I.V. parecoxib 40 mg, once only, 2 h following the end of surgery	Not specified	I.V. pethidine

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Table 1. Continued

Reference	Group (n)	Journal title	Language	Country of the enrolled patients	Nature of cesarean section	Mode of anesthesia	Intraoperative regional anesthesia and systemic analgesia	Dose, route, and timing of NSAID administration	Regular postoperative analgesia	Management of postoperative breakthrough pain
Control vs tenoxicam										
Belzarena 1994 [56]	Control (40) Tenoxicam (40)	Regional Anesthesia	English	Brazil	Elective; surgical approach not specified	Spinal	Spinal: 3 ml 0.5% hyperbaric bupivacaine	I.V. tenoxicam 20 mg, once only, before spinal anesthesia	Not specified	Paracetamol and codeine of unspecified route
Elhakim and Nafie 1995 [58]	Control (25) Tenoxicam (25)	British Journal of Anaesthesia	English	Egypt	Elective; surgical approach not specified	General anesthesia	Systemic: I.V. nalbuphine 0.25 mg/kg	I.V. tenoxicam 20 mg, once only, before induction of general anesthesia	None	I.M. nalbuphine
Ro et al. 1997 [59]	Control (20) Tenoxicam (20)	Korean Journal of Anesthesiology	Korean	Korea	Not specified	General anesthesia	None	I.V. tenoxicam 0.3 mg/kg, once only, before induction of general anesthesia	I.V. morphine 0.1 mg/kg bolus followed by infusion of 0.015 mg/kg/h	Not specified
Huang et al. 2002 [60]	Control (59) Tenoxicam (58)	Canadian Journal of Anaesthesia	English	Taiwan, Republic of China	Elective; surgical approach not specified	Spinal	Spinal: 1.8–2.2 ml 0.5% hyperbaric bupivacaine with morphine 150 μg	I.V. tenoxicam 40 mg, once only, following clamping of umbilical cord	Not specified	I.M. pethidine
Hsu et al. 2003 [61]	Control (48) Tenoxicam (45)	Clinical Journal of Pain	English	Taiwan, Republic of China	Elective; surgical approach not specified	Spinal	Spinal: 12.5 mg bupivacaine of unspecified baricity, concentration, and volume	I.V. tenoxicam 20 mg, once only, following clamping of umbilical cord	I.V. morphine PCA	Not specified
Yeh et al. 2005 [62]	Control (40) Tenoxicam (40)	Journal of the Formosan Medical Association	English	Taiwan, Republic of China	Elective; Pfannensteil approach	Spinal	Spinal: 1.8–2.2 ml 0.5% hyperbaric bupivacaine	I.V. tenoxicam 20 mg, once only, following clamping of umbilical cord	I.V. morphine PCA	Not specified
Diclofenac vs ketoprofen										
Hirahara et al. 2003 [63]	Diclofenac (22) Ketoprofen (22)	Revista Brasileira de Anestesiologia	English	Brazil	Not specified	Spinal	Spinal: 3 ml 0.5% hyperbaric bupivacaine with morphine 28 μg	I.M. diclofenac 75 mg or I.V. ketorolac 100 mg, once only, 90 min after spinal anesthesia	I.V. morphine PCA	Not specified
Ketorolac vs parecoxib										
Wong et al. 2010 [64]	Ketorolac (33) Parecoxib (33)	Acta Anaesthesiologica Taiwanica	English	Taiwan, Republic of China	Elective; surgical approach not specified	Spinal	Not specified	I.V. parecoxib 40 mg in recovery room and two further doses at 24 h and 48 h, or I.V. ketorolac 30 mg in recovery room followed by I.V. ketorolac in morphine PCA, administered at a rate of 0.36 mg/h and patient-controlled bolus of 1.8 mg with an unspecified time interval	I.V. morphine PCA	I.V. morphine

CSE: combined spinal-epidural, PCA: patient-controlled analgesia, PO: per oral, IV: intravenous, PR: per rectum, IM: intramuscular.

perior to celecoxib + parecoxib for the rate of in-hospital pruritus, and diclofenac was clinically and statistically superior to control for the rate of sedation at 24 h and in-hospital. The hospital length of stay was statistically but not clinically different between diclofenac and control.

Discussion

Our systematic review and network meta-analysis demonstrated that, compared to control, the administration of diclofenac, indomethacin, ketorolac, or tenoxicam led to a clinically significant decrease in the primary outcome, namely cumulative morphine consumption at 24 h, using an MCID of 10 mg. The quality of evidence, however, was very low due to serious limitations, imprecision, and publication bias. Differences between various NSAIDs were found, with indomethacin clinically superior to celecoxib and celecoxib + parecoxib, diclofenac, and ketorolac for the pain score at rest at 8–12 h and the pain score on movement at 48 h, respectively, when an MCID of 10 on a pain scale of 0–100 was applied. Indomethacin may be preferable, although it must be recognized that the evidence for other NSAIDs continues to emerge and is currently limited by the presence of imprecision.

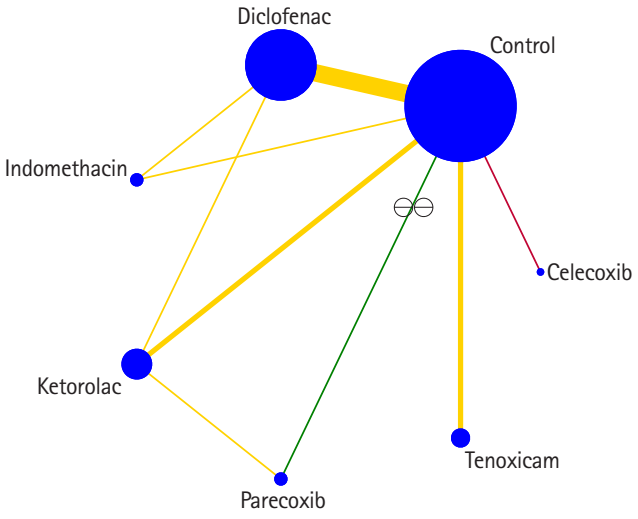

Fig. 3. Network plot in regard to the need for cumulative intravenous morphine equivalent consumption at 24 h. Each intervention is depicted by a circle that is proportional in size to the number of patients who were randomized to that intervention. Connecting lines between the circles indicate the direct comparisons of interventions, their width proportional to the number of trials evaluating the comparison, and their color representing the average risk of bias. Green: low risk, yellow: some concerns, red: high risk.

In contrast to diclofenac, indomethacin, ketorolac, and tenoxicam, control was not inferior to other NSAIDs such as celecoxib and parecoxib for the cumulative morphine consumption at 24 h. It is likely that this could be a reflection of the limited evidence base for these NSAIDs, resulting in imprecision and wide CIs, and the different dosing regimens employed in the included trials. In many trials that investigated diclofenac, indomethacin, and ketorolac, more than one dose of the NSAID was administered in 24 h [25,27–33,37,38,40,42–45,48,50–53]. Further, tenoxicam has a long mean elimination half-life of 67 h [70], explaining its beneficial effects on morphine consumption despite only being given once in the relevant trials [56,58–62]. Similarly, the various dosing strategies in the included trials may explain, at least in part, the superiority of ketoprofen to celecoxib + parecoxib in regard to the need for rescue analgesia and diclofenac, indomethacin, and ketorolac, but not ibuprofen, over celecoxib with respect to the time to rescue analgesia. Selective COX-2 inhibitors such as celecoxib have gained popularity as effective analgesics, particularly as they can produce fewer gastrointestinal side effects [71]. Their inferi-

Table 2. Network League Table for All the Interventions in regard to Cumulative Intravenous Morphine Equivalent Consumption at 24 h

Celecoxib						
−14.21 (−36.00, 7.58)	Control					
5.66 (−17.31, 28.64)	19.87 (12.56, 27.18)*	Diclofenac				
7.07 (−21.96, 36.10)	21.28 (2.09, 40.47)*	1.41 (−17.78, 20.59)	Indomethacin			
−1.68 (−26.32, 22.96)	12.53 (1.00, 24.05)*	−7.34 (−20.34, 5.65)	−8.75 (−30.94, 13.44)	Ketorolac		
−6.12 (−33.53, 21.30)	8.09 (−8.57, 24.75)	−11.78 (−29.74, 6.18)	−13.19 (−38.51, 12.14)	−4.44 (−21.26, 12.39)	Parecoxib	
0.46 (−24.86, 25.78)	14.67 (1.74, 27.59)*	-5.20 (−20.05, 9.64)	−6.61 (−29.75, 16.53)	2.14 (−15.18, 19.46)	6.57 (−14.51, 27.66)	Tenoxicam

Estimates are presented as mean differences with 95% CI in parentheses. Mean differences below 0 favor the column intervention and mean differences above 0 favor the row intervention. *Interventions which are significantly different since the 95% CI does not include 0.

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Table 3. Conclusion from the Results of the Analysis and GRADE Quality of Evidence Assessment for the Primary and Secondary Outcomes

Outcome	Number of trials	Total number of participants	Number of direct comparisons	Number of indirect comparisons	MCID	Conclusions	Quality of evidence	Comments
Analgesia								
Pain score at rest at 8–12 h (0–100) [11,23,25,26,34,35,37,42,43,45,47–49,57,59,61–63]	18	1,523	8	20	10	Control clinically and statistically inferior to diclofenac and indomethacin Indomethacin clinically and statistically superior to celecoxib No other statistical differences between interventions, but, with MCID of 10, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Pain score on movement at 8–12 h (0–100) [11,25,30,42,47,52,57]	7	506	6	4	10	Control statistically inferior but clinically equivalent to diclofenac No statistical differences between interventions, but, with MCID of 10, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Pain score at rest at 24 h (0–100) [11,23,25,34,37,38,41–45,47–49,56,59,61–65,67]	22	1,790	9	19	10	Control clinically and statistically inferior to diclofenac Control statistically inferior but clinically equivalent to tenoxicam No other statistical differences between interventions, but, with MCID of 10, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Pain score on movement at 24 h (0–100) [11,25,30,42,44,47,52,55,64]	9	582	5	10	10	Control clinically and statistically inferior to diclofenac No other statistical differences between interventions, but, with MCID of 10, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Pain score at rest at 48 h (0–100) [25,34,37,43,45,62]	6	571	3	3	10	No statistical differences between interventions, but, with MCID of 10, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Pain score on movement at 48 h (0–100) [25,30,52,55]	4	235	4	6	10	Control clinically and statistically inferior to indomethacin No clinical or statistical difference between control and celecoxib + parecoxib Indomethacin clinically and statistically superior to celecoxib + parecoxib, diclofenac and ketorolac No other statistical differences between interventions, but, with MCID of 10, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision

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Table 3. Continued

Outcome	Number of trials	Total number of participants	Number of direct comparisons	Number of indirect comparisons	MCID	Conclusions	Quality of evidence	Comments
Need for rescue analgesia (%) [23,25–28,32,37,40,43,47,51,53–55,57–60,63,66]	20	1,586	10	35	20%	Control statistically and clinically inferior to diclofenac, ketoprofen and tenoxicam Ketoprofen statistically and clinically superior to celecoxib + parecoxib No other statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Very low quality (⊕)	Downgraded for serious limitations, imprecision, and publication bias
Time to rescue analgesia (min) [10,11,24,30,40,46,49–52,54,55,57,58,60]	15	1,076	10	18	60 min	Control clinically and statistically inferior to diclofenac, ketorolac and naproxen Diclofenac, ibuprofen, indomethacin and ketorolac clinically and statistically superior to celecoxib No other statistical differences between interventions, but, with MCID of 60 min, clinical differences possible	Very low quality (⊕)	Downgraded for serious limitations, imprecision, inconsistency, and publication bias
Cumulative intravenous morphine equivalent consumption at 8–12 h (mg) [26,33–35,39,55]	6	364	2	1	10 mg	Control clinically and statistically inferior to diclofenac No other statistical differences between interventions, but, with MCID of 10 mg, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Cumulative intravenous morphine equivalent consumption at 24 h (mg) [24,33–35,38–40,42,44,49,50,54,56,59,61,64,65,67]	18	1,228	9	12	10 mg	Control clinically and statistically inferior to diclofenac, indomethacin, ketorolac and tenoxicam No other statistical differences between interventions, but, with MCID of 10 mg, clinical differences possible	Very low quality (⊕)	Downgraded for serious limitations, imprecision and publication bias
Cumulative intravenous morphine equivalent consumption at 48 h (mg) [31,33,34]	3	320	-	-	10 mg	Pairwise comparison only Control clinically and statistically inferior to diclofenac (MD: -46.29, 95% CI [-60.71, -31.86], I^2 = 73%; P < 0.0001)	Moderate quality (⊕⊕⊕)	Downgraded for serious limitations
Cumulative in-hospital intravenous morphine equivalent consumption (mg) [29,31,41,55,67]	5	404	3	3	10 mg	Control clinically and statistically inferior to diclofenac, ketorolac and parecoxib No other statistical differences between interventions, but, with MCID of 10 mg, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Side effects								
Rate of postoperative nausea and/or vomiting at 24 h (%) [10,29,36,39–41,44,48,53,55,61,64,67]	13	938	4	6	20%	No statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision

(Continued to the next page)

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Table 3. Continued

Outcome	Number of trials	Total number of participants	Number of direct comparisons	Number of indirect comparisons	MCID	Conclusions	Quality of evidence	Comments
Rate of postoperative nausea and/or vomiting at 48 h (%) [52,55]	2	74	2	1	20%	No statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Very low quality (⊕)	Downgraded for serious limitations, imprecision and publication bias
Rate of in-hospital postoperative nausea and/or vomiting (%) [27,28,30–34,38,42,45,47,54,57,60,62,63,66]	17	1,387	4	6	20%	No statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Rate of pruritus at 24 h (%) [52,53,55,64,67]	5	293	4	6	20%	No statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Rate of pruritus at 48 h (%) [52,55]	2	74	2	1	20%	No statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Very low quality (⊕)	Downgraded for serious limitations, imprecision and publication bias
Rate of in-hospital pruritus (%) [23,25,27,28,30,31,34,36,38,54,60,62,63,66]	14	1,043	6	15	20%	Ketoprofen statistically and clinically superior to celecoxib + parecoxib No other statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Rate of sedation at 24 h (%) [29,36,37,40,48,55,61,67]	8	630	4	6	20%	Control statistically and clinically inferior to diclofenac No other statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Rate of sedation at 48 h (%) [55]	1	44	-	-	20%	In one trial, no statistical difference between control and ketorolac	-	-
Rate of in-hospital sedation (%) [31,33,34,38,45]	5	559	-	-	20%	Pairwise comparison only Control clinically and statistically inferior to diclofenac (RR: 0.43, 95% CI [0.26, 0.73], I^2 = 13; P = 0.002)	Moderate quality (⊕⊕⊕)	Downgraded for serious limitations
Functional outcomes								
Hospital length of stay (h) [39,44,48,67]	4	317	-	-	6 h	Pairwise comparison Control statistically inferior but clinically equivalent to diclofenac (MD: -0.48, 95% CI [-0.88, -0.08], I^2 = 0%; P = 0.02) In one trial, no statistical difference between ketorolac and parecoxib	Moderate quality (⊕⊕⊕)	Downgraded for serious limitations

GRADE: grading of recommendations assessment development and evaluation, MCID: minimally clinically important difference, MD: mean difference, RR: risk ratio.

ority to other NSAIDs could be indicative of their slow absorption from the small intestine following oral administration [72], and their relatively homogenous distribution in body tissue in comparison to acetic acid derivatives with acidic functional groups such as diclofenac, ketorolac, and indomethacin. NSAIDs that are acetic acid derivatives as well as those with high protein binding can selectively accumulate and persist in areas of inflammation [72,73], and this may facilitate their increased analgesic effectiveness at sites of tissue injury subsequent to cesarean section. The superiority of indomethacin to other NSAIDs might be representative of its potential to act as a positive allosteric modulator at the type one cannabinoid receptor, modifying the endocannabinoid system and increasing its antinociceptive properties [74].

In terms of side effects, diclofenac compared to control resulted in decreased sedation at 24 h and in-hospital. This probably underlines its capacity to influence the pain score at 8–12 h and 24 h as well as the need for and time to rescue analgesia, hence reducing the cumulative morphine consumption and these secondary undesirable effects. Interestingly, in the absence of differences in the cumulative morphine consumption, ketoprofen decreased the rate of in-hospital pruritus compared to celecoxib + parecoxib. NSAIDs do not have any recognized direct antipruritic effects [75], and it is possible that the lack of difference in the cumulative morphine consumption was once again a reflection of imprecision rather than absence of true underlying differences.

Our findings corroborate and expand upon the systematic reviews and meta-analyses conducted to date. Consistent with what we have shown, in a prior meta-analysis of 22 randomized controlled trials, NSAIDs were reported to be superior to control in the context of cesarean section for the pain score at 12 h and 24 h and the cumulative morphine consumption [8]. NSAIDs have been compared in settings outside that of cesarean section in other systematic reviews [76–78]. In a previous network meta-analysis of 26 randomized controlled trials, etoricoxib was superior to celecoxib, ketoprofen, and tenoxicam for pain relief in ankylosing spondylitis [76], and in a prior systematic review of 76 randomized controlled trials, diclofenac, etoricoxib, and rofecoxib were ranked highest for the reduction of pain in hip and knee osteoarthritis [77].

We acknowledge the limitations related to this meta-analysis. First, there were a limited number of trials comparing different NSAIDs. Second, few trials were evaluated to be at low risk of bias, and concerns were present in the remaining trials in regard to the randomization process, measurements of the outcome, and the selection of the reported result. Third, the included trials investigated patients who had emergency and/or elective cesarean section under neuraxial, with or without intrathecal opioids, or general anesthesia. Moreover, the strategy of NSAID administration was inconsistent with varied dosing, route, and duration. Such variability introduces heterogeneity, although it increases the generalizability of the findings. Fourth, the standard practice of multimodal analgesia with paracetamol was, surprisingly, only used in a minority of trials. The combination of paracetamol and NSAIDs has been recommended due to their additive effect [79,80]. Fifth, a change in the pain score of 10 on a pain scale of 0–100, including in obstetrics, has been revealed to represent a clinically important difference in the intensity of pain [81]. It is likely, however, that the MCID for any individual patient may vary depending on the severity of the pain, with a greater MCID needed for more severe pain [82]. The MCID for many indices remains undetermined in cesarean section [83], and the authors thus used their experience in this systematic review to select the different thresholds for clinical significance. Sixth, concerns with respect to imprecision for most outcomes precluded the ranking of various NSAIDs. Last, we did not examine which NSAID was best in terms of minimizing transfer to breast milk and increasing safety in breastfeeding women. Those NSAIDs with low oral bioavailability, high protein binding, short half-life, and inactive metabolites as well as reassuring data on breast milk transfer and long record of safe use are likely to be optimal in this respect [80,84]. Interestingly, ibuprofen is thought to be the ideal NSAID for women who are breastfeeding, but our results do not provide sufficient data to confirm its superior properties in the context of cesarean section.

Our network meta-analysis and systematic review demonstrated that diclofenac, indomethacin, ketorolac, and tenoxicam compared to control decreased cumulative morphine consumption at 24 h. No differences were found between different NSAIDs in the cumulative morphine consumption at 24 h, and the quality of evidence was very low. Differences in the secondary outcomes between various NSAIDs were uncovered, with indomethacin clinically superior to celecoxib and celecoxib + parecoxib, diclofenac, and ketorolac for the pain score at rest at 8–12 h and the pain score on movement at 48 h. In light of this emerging but limited evidence, our review suggests the presence of minimal differences among the NSAIDs studied. Nonselective NSAIDs may be more effective than selective NSAIDs, and some NSAIDs such as indomethacin might be preferable to other NSAIDs. Further trials with designs relevant to modern obstetric anesthesia practice are required to increase the strength and quality of the evidence base and the recommendations related to the selection of NSAIDs in the setting of cesarean section.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

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Supplementary Materials

Supplementary Material 1. Search Strategy.
Supplementary Material 2. GRADE quality of evidence assessment for each outcome.
Supplementary Material 3. Network league table for secondary outcomes.
Supplementary Material 4. Statistical analysis.
Supplementary Fig. 1. Comparison-adjusted funnel plot with respect to the network for cumulative morphine equivalent consumption at 24 h. Different colors correspond to particular comparisons of interventions. The red line indicates the null hypothesis that the comparison-specific pooled effect estimates do not differ from the respective trial-specific effect sizes.

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Effect of magnesium sulfate on oxygenation and lung mechanics in morbidly obese patients undergoing bariatric surgery: a prospective double-blind randomized clinical trial

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Background: Respiratory mechanics are often significantly altered in morbidly obese patients and magnesium sulfate ($MgSO_4$) is a promising agent for managing several respiratory disorders. This study aimed to examine the effects of $MgSO_4$ infusions on arterial oxygenation and lung mechanics in patients with morbid obesity undergoing laparoscopic bariatric surgery.

Methods: Forty patients with morbid obesity aged 21–60 years scheduled for laparoscopic bariatric surgery under general anesthesia were randomly allocated to either the control (normal saline infusion) or $MgSO_4$ group (30 mg/kg lean body weight [LBW] of 10% $MgSO_4$ in 100 ml normal saline intravenously over 30 min as a loading dose, followed by 10 mg/kg LBW/h for 90 min). The primary outcome was intraoperative arterial oxygenation (Δ PaO_2/FiO_2). Secondary outcomes included intraoperative static and dynamic compliance, dead space, and hemodynamic parameters.

Results: At 90 min intraoperatively, the Δ PaO_2/FiO_2 ratio and the Δ dynamic lung compliance were statistically significantly higher in the $MgSO_4$ group (mean ± SE: 16.1 ± 1.0, 95% CI [14.1, 18.1] and 8.4 ± 0.5 ml/cmH_2O, 95% CI [7.4, 9.4]), respectively), and the Δ dead space (%) was statistically significantly lower in the $MgSO_4$ group (mean ± SE: −8.0 ± 0.3%, 95% CI [−8.6, −7.4], $P < 0.001$). No significant differences in static compliance were observed.

Conclusions: Although $MgSO_4$ significantly preserved arterial oxygenation and maintained dynamic lung compliance and dead space in patients with morbid obesity, the clinical relevance is minimal. This study failed to adequately reflect the clinical importance of these results.

Keywords: Anesthesia; Bariatric surgery; Laparoscopy; Magnesium sulfate; Morbid obesity; Respiratory mechanics.

Introduction

Bariatric surgery is considered the most effective treatment for patients with morbid obesity as it results in weight loss and has a clear impact on obesity-related comorbidities [1].

Morbid obesity is commonly associated with a higher incidence of restrictive lung diseases [2]. Obese patients often exhibit significant alterations in respiratory mechanics, which can be further aggravated by general anesthesia, such as decreased expirato-

ry reserve volume (ERV) and functional residual capacity (FRC). In addition to atelectasis, insufficient oxygenation, reduced chest and lung compliance, increased lung resistance, and increased work of breathing have been reported [3,4].

Additionally, morbid obesity is often associated with respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD). A meta-analysis of more than 300,000 adult patients found a direct relationship between obesity and asthma, suggesting that as the body mass index (BMI) increases, the risk of asthma increases [5]. The mechanisms underlying this relationship may include the mechanical consequences of long-term lung compression, exaggerated local and systemic inflammation, and abnormal immunological responses, which are usually altered in obesity [6]. Moreover, obesity is more prevalent among patients with COPD than in the general population [7]. Hence, obese patients are more prone to postoperative acute respiratory failure [8] and have a higher incidence of pneumonia, prolonged periods of mechanical ventilation, and weaning difficulty [9–14].

Magnesium sulfate ($MgSO_4$) is a promising agent with favorable effects in the management of various respiratory disorders such as asthma, COPD, and pulmonary hypertension. Endogenous magnesium plays a crucial role in sustaining appropriate lung function and reducing airway reactivity [15,16]. Magnesium helps smooth muscle relaxation by blocking calcium release [17]. It also acts through various mechanisms such as T cell stabilization, prevention of mast cell degranulation, inhibition of acetylcholine release, and stimulation of nitric oxide and prostacyclin synthesis, thereby reducing airflow obstruction [17]. Several studies have reported magnesium deficiency in patients with asthma [18]. Furthermore, low serum magnesium levels are associated with COPD exacerbation [19].

A recent study found promising results regarding arterial oxygenation and lung mechanics with the administration of intraoperative magnesium in patients with COPD [20]. We hypothesized that magnesium supplementation could improve perioperative oxygenation and lung mechanics parameters in morbidly obese patients undergoing bariatric surgery. Therefore, this study aimed to examine the effects of intraoperative $MgSO_4$ administration on arterial oxygenation and lung mechanics in morbidly obese patients undergoing bariatric surgery.

Materials and Methods

This double-blind, randomized clinical trial was approved by the Research Ethical Committee of the Faculty of Medicine, Ain Shams University (Approval number: FMASU R07/2021), and registered at ClinicalTrials.gov (NCT04769440). This study was also conducted in accordance with the ethical principles of the Helsinki Declaration 2013. A total of 40 patients aged 21–60 years with a BMI > 40 kg/m^2 and restrictive lung disease diagnosed by pulmonary function tests (forced vital capacity [FVC] < 70%) were enrolled. The included patients were scheduled for laparoscopic bariatric surgery < 3 h under general anesthesia and had no previous history of abdominal surgery.

The exclusion criteria were as follows: refusal to participate in the study; American Society of Anesthesiologists (ASA) physical status score > II; history of organ failure (e.g., cardiac, hepatic, or renal), arrhythmias, or combined restrictive-obstructive pulmonary disease; or use of antiarrhythmic drugs, beta-blockers, or calcium channel blockers. Patients with any of the following were also excluded from the study: forced expiratory volume in the first second (FEV1)/FVC < 70%, pregnancy or lactation, a history of allergies to the study drugs, and operation time > 3 h.

This study was conducted at hospitals affiliated with Ain Shams University between March 2021 and February 2022. After all patients who met the inclusion criteria provided informed consent, they were randomly assigned to either the $MgSO_4$ group or the control group at a 1 : 1 ratio using a computer-generated table of random numbers sealed in opaque envelopes. The envelopes were opened immediately before drug administration. Fifteen minutes after endotracheal intubation, the patients in the $MgSO_4$ group (n = 20) received an intravenous infusion of 10% $MgSO_4$ in 100 ml normal saline at 30 mg/kg lean body weight (LBW) over 30 min as a loading dose, followed by 10 mg/kg LBW/h for 90 min. Patients in the control group (n = 20) received an intravenous infusion of 100 ml of normal saline for 30 min, followed by a saline infusion at the same rate as the study group for 90 min. The study drugs were prepared by hospital pharmacists. Moreover, a blinded anesthetist who did not participate in the study performed patient follow-up.

Preoperatively, each patient's medical history and demographic data (i.e., age, BMI, and ASA physical status score) were recorded, and a thorough physical examination was performed, including complete blood count, prothrombin time, activated partial thromboplastin time, liver and kidney function tests, serum magnesium levels, pulmonary function tests, and arterial blood gases. Patients were instructed to fast for 8 h before the operation.

Upon arrival in the operating room, an intravenous cannula was inserted. The patient was premedicated with ranitidine (50 mg) and metoclopramide (10 mg). Standard monitoring via noninvasive blood pressure (NIBP), electrocardiography (ECG), and pulse oximetry was conducted for all patients, and capnography was performed after intubation. Baseline readings of the mean arterial pressure (MAP), heart rate (HR), and oxygen saturation

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(SpO_2) were also recorded.

LBW was used to calculate the doses of all drugs except neostigmine, for which total body weight was used. LBW was calculated using the James equation as follows: (1.10 × weight) – (128 [weight/height]^2) for men and (1.07 × weight) – (148 [weight/height]^2) for women [21].

Preoxygenation was performed for 5 min. Anesthesia was induced by slowly administering intravenous fentanyl (2 μg/kg LBW) and propofol (1.5–2 mg/kg LBW) until loss of response to verbal commands. Intravenous atracurium (0.5 mg/kg LBW) was administered to facilitate tracheal intubation. Anesthesia was maintained with 1.0%–1.5% isoflurane in oxygen at a fraction of inspired oxygen (FiO_2) of 0.4. In the event that the SpO_2 dropped below 95%, the FiO_2 was increased gradually by 0.1. The neuromuscular block was maintained with incremental doses of atracurium (0.01 mg/kg LBW) every 30 min, guided by peripheral nerve stimulator monitoring while maintaining a train-of-four (TOF) count at 1/4. All the measurements were performed using a TOF count of 1/4.

All the patients were mechanically ventilated. We adopted a volume-controlled mode of ventilation, maintaining a low tidal volume of 6–8 ml/kg LBW, and positive end-expiratory pressure (PEEP) ranging from 8 to 10 cmH_2O. End-tidal CO_2 was maintained between 30 and 35 mmHg by adjusting the respiratory rate.

The patients were placed in the reverse Trendelenburg position and the abdomen was insufflated with CO_2, maintaining an intra-abdominal pressure between 14 and 15 mmHg. Ringer's acetate was administered during the operation, and the total volume of consumed fluids was calculated. All the surgical procedures were performed by the same team. Intravenous paracetamol (2 g) and ketorolac (40 mg) were administered at the end of surgery. The surgeon then carefully evacuated the CO_2 from the abdomen, and the isoflurane treatment was discontinued. Muscle relaxation was reversed prior to extubation. Once the TOF count reached 2/4, neostigmine 0.05 mg/kg and atropine 0.02 mg/kg LBW were administered to counteract the remaining muscle relaxant effect. Once the patients were able to follow verbal commands, they were transferred to the post-anesthesia care unit (PACU), where they were closely monitored.

Outcomes

To evaluate the primary and secondary outcomes, the following variables were recorded.

Primary outcome

To assess the primary outcome of intraoperative arterial oxygenation, we evaluated the Δ PaO_2/FiO_2. The PaO_2/FiO_2 ratio was recorded 5 min after endotracheal intubation (baseline) and 90 min after the drug infusion was initiated. The Δ PaO_2/FiO_2 ratio was calculated by subtracting the PaO_2/FiO_2 ratio at baseline from the PaO_2/FiO_2 ratio 90 min after initiating the drug infusion.

Secondary outcomes

To evaluate the secondary outcomes, static and dynamic lung compliance, dead space, and hemodynamic parameters were assessed. Static lung compliance was calculated as: tidal volume/(plateau pressure – PEEP). Dynamic lung compliance was calculated as: tidal volume / (peak airway pressure – PEEP). Physiological dead space was calculated as Vd/Vt = 1.14 ($PaCO_2$ – $EtCO_2$)/($PaCO_2$ – 0.005) using the Hardman and Aitkenhead equation [22]. Each was recorded 5 min after endotracheal intubation (baseline) and 90 min after initiating the drug infusion. The Δ static compliance was calculated by subtracting the static lung compliance at baseline from the static lung compliance 90 min after initiating the drug infusion. The Δ dynamic compliance was calculated by subtracting the dynamic lung compliance at baseline from the dynamic lung compliance 90 min after initiating the drug infusion. Finally, the Δ dead space (%) was calculated as follows: dead space 90 min after initiating the drug infusion – dead space at baseline/dead space at the end of the drug infusion%.

To assess hemodynamic parameters, the MAP and HR were recorded at baseline and every 15 min. In the event that the MAP dropped > 20% from baseline, vasoactive medications such as ephedrine were administered, and atropine was administered if the HR dropped to < 50 beats/min. The Ramsay sedation score was assessed upon arrival in the operating room, immediately postoperatively, and 1 h postoperatively [23]. Serum $MgSO_4$ levels were recorded 1 h postoperatively.

The following operative data were recorded: surgical time, intraoperative fluids, blood loss, recovery time (defined as the time from the cessation of isoflurane to the patient complying with orders), and the need for postoperative intensive care unit (ICU) admission (criteria for admission were SpO_2 < 88% on a 6-L oxygen mask, signs of altered consciousness [agitation or drowsiness], tachypnea, and the need for postoperative mechanical ventilation). Postoperative complications such as bleeding or leakage were also recorded. Patients were transferred to the hospital ward if the modified Aldrete score was ≥ 9.

Sample size calculation

Using the PASS 11 and setting the power to 0.80 and α to 0.05, a minimal sample size of two cases in each group was required to

obtain statistically significant results between the assumed Δ PaO_2/FiO_2 (%) in the $MgSO_4$ and control groups (Δ 3.1 ± 0.2 and −12.2 ± 0.5, respectively) [20]. A sample size of 40 patients (20 patients per group) was used to ensure that the sample was representative of the entire population.

Statistical analysis

IBM Statistical Package for Social Sciences (SPSS) statistics software (version 22.0; IBM Corp., USA) was used to code, tabulate, and statistically analyze the collected data. Quantitative data were tested for normality using the Shapiro-Wilk test. Normally distributed data were compared using the independent t-test (group comparisons) and paired t-test (time comparisons) and are described using the mean ± standard deviation (SD). Non-normally distributed data were compared using the Mann-Whitney test and are described using the median (first – third interquartile range). Qualitative data were compared using Fisher's exact test and are presented as numbers and percentages. The level of significance was set at a $P < 0.05$.

Results

While 49 individuals were recruited for this study, eight patients did not meet the study's inclusion criteria and one patient declined to participate. Thus, a total of 40 patients were included in this study. The patients were divided into two groups of 20 patients each (Fig. 1). Baseline characteristics (age, BMI, FVC, FEV1/FVC ratio, intraoperative fluids, blood loss, operation duration, and baseline $MgSO_4$ levels) were not statistically significantly different between the groups (Table 1).

In terms of intraoperative oxygenation, the PaO_2/FiO_2 ratio decreased significantly among patients in the control group at 90 min intraoperatively compared with baseline, whereas no significant decrease was observed among patients in the $MgSO_4$ group at 90 min intraoperatively compared with baseline. Additionally, the PaO_2/FiO_2 ratio at 90 min was not significantly different between the groups; however, the Δ PaO_2/FiO_2 ratio at 90 min increased in the $MgSO_4$ group compared to the control group (mean ± SD: −0.8 ± 1.8 vs. −16.9 ± 3.9, respectively), with a statistically significant difference (mean ± SE: 16.1 ± 1.0, 95% CI [14.1, 18.1], $P < 0.001$; Table 2).

In terms of lung mechanics, static compliance was not significantly different between the two groups at baseline or at 90 min

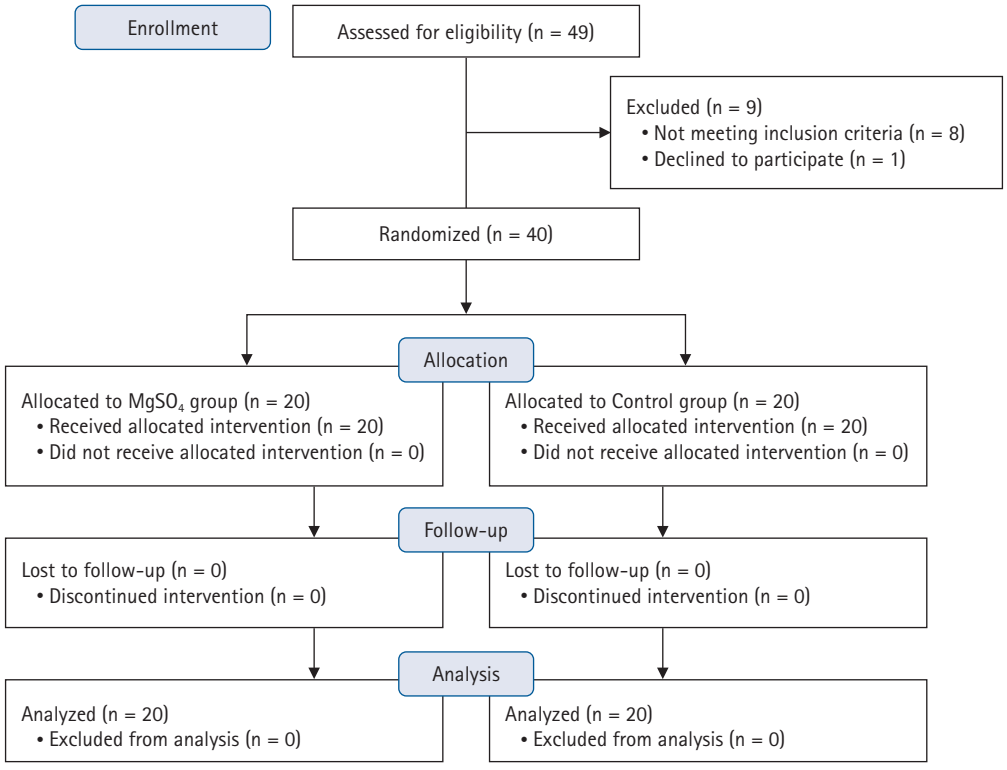

Fig. 1. CONSORT patient selection flowchart.

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Table 1. Comparison of Baseline Characteristics between the Study Groups

Variable	$MgSO_4$ group (n = 20)	Control group (n = 20)	P value
Age (yr)	32.4 ± 4.5	33.7 ± 4.2	0.334
BMI (kg/m^2)	49.2 ± 2.2	48.5 ± 2.7	0.367
FVC	62.8 ± 1.3	63.3 ± 1.4	0.304
FEV1/FVC	78.5 ± 1.5	79.1 ± 2.0	0.292
Intraoperative fluids (ml)	872.0 ± 39.1	884.0 ± 42.4	0.358
Blood loss (ml)	243.5 ± 49.0	257.5 ± 49.7	0.376
Operation duration (min)	121.8 ± 11.0	118.4 ± 11.0	0.334
Baseline $MgSO_4$ (mg/dl)	1.6 ± 0.3	1.5 ± 0.3	0.622

Values are presented as mean ± SD. $MgSO_4$ group: magnesium sulfate infusion group, Control group: normal saline infusion group. BMI: body mass index, FVC: forced vital capacity, FEV1: forced expiratory volume in one second.

Table 2. Comparison of Intraoperative Oxygenation between the Study Groups

Parameter	Time	$MgSO_4$ group (n = 20)	Control group (n = 20)	P value*	Effect size	
					Mean ± SE	95% CI
Intraoperative oxygenation (PaO_2/FiO_2 ratio)	Baseline	317.7 ± 24.1	315.5 ± 40.2	0.832	2.3 ± 10.5	−19.1, 23.6
	Minute 90	316.9 ± 23.5	298.6 ± 41.1	0.093	18.4 ± 10.6	−3.3, 40.0
	P value†	0.057	< 0.001‡			
	Δ Minute 90	−0.8 ± 1.8	−16.9 ± 3.9	< 0.001‡	16.1 ± 1.0	14.1, 18.1

Values are presented as mean ± SD. $MgSO_4$ group: magnesium sulfate infusion group, Control group: normal saline infusion group. PaO_2: partial pressure of oxygen in arterial blood, FiO_2: fraction of inspired oxygen concentration, Δ: delta (time – baseline). Effect size: value of $MgSO_4$ relative to control. *Comparison between the groups. †Comparison within groups. ‡P value < 0.05; statistically significant.

Table 3. Comparison of Lung Mechanics between the Study Groups

Parameter	Time	$MgSO_4$ group (n = 20)	Control group (n = 20)	P value*	Effect size	
					Mean ± SE	95% CI
Static compliance (ml/cmH_2O)	Baseline	42.9 ± 5.0	41.2 ± 3.8	0.235	1.7 ± 1.4	−1.2, 4.6
	Minute 90	42.7 ± 4.8	40.9 ± 3.4	0.181	1.8 ± 1.3	−0.9, 4.5
	P value†	0.096	0.069			
	Δ Minute 90	−0.2 ± 0.6	−0.4 ± 0.8	0.515	0.2 ± 0.2	−0.3, 0.6
Dynamic compliance (ml/cmH_2O)	Baseline	41.6 ± 6.1	39.7 ± 4.9	0.297	1.8 ± 1.7	−1.7, 5.4
	Minute 90	41.3 ± 6.0	31.1 ± 5.5	< 0.001‡	10.3 ± 1.8	6.6, 13.9
	P value†	0.056	< 0.001‡			
	Δ Minute 90	−0.3 ± 0.6	−8.7 ± 2.1	< 0.001‡	8.4 ± 0.5	7.4, 9.4
Dead space (%)	Baseline	18.4 ± 3.6	17.3 ± 3.3	0.321	1.1 ± 1.1	−1.1, 3.3
	Minute 90	18.2 ± 3.8	25.1 ± 3.3	< 0.001‡	−6.9 ± 1.1	−9.2, −4.6
	P value†	0.204	< 0.001‡			
	Δ Minute 90	−0.3 ± 0.9	7.8 ± 1.1	< 0.001‡	−8.0 ± 0.3	−8.6, −7.4

Values are presented as mean ± SD. $MgSO_4$ group: magnesium sulfate infusion group, Control group: normal saline infusion group. Δ: delta (time – baseline). Effect size: value of $MgSO_4$ relative to control. *Independent t-test (comparison between groups), †Repeated measures ANOVA (comparison within groups), ‡P value <0.05 was considered statistically significant.

intraoperatively. In addition, static compliance at 90 min compared to baseline was not significantly different between the two groups (Table 3). In contrast, dynamic compliance was significantly higher in the $MgSO_4$ group than in the control group at 90 min intraoperatively (P < 0.001). Although dynamic compliance decreased significantly at 90 min in the control group compared to baseline (P < 0.001), no significant difference was found at 90 min in the $MgSO_4$ group compared to baseline (Table 3).

In terms of dead space, no significant differences were observed in the $MgSO_4$ group at 90 min intraoperatively compared to baseline, whereas a significant increase was observed in the control group (P < 0.001). In the between-group comparison, the dead

space was significantly higher in the control group than in the $MgSO_4$ group at 90 min postoperatively (P < 0.001) (Table 3). The Δ dynamic lung compliance was higher in the $MgSO_4$ group than in the control group at 90 min intraoperatively (mean ± SD: −0.3 ± 0.6 ml/cmH_2O vs. −8.7 ± 2.1 ml/cmH_2O, respectively), with a statistically significant difference (mean ± SE: 8.4 ± 0.5 ml/cmH_2O, 95% CI [7.4, 9.4], P < 0.001). Additionally, the Δ dead space (%) was lower in the $MgSO_4$ group than in the control group (mean ± SD: −0.3 ± 0.9% vs. 7.8 ± 1.1%, respectively), with a statistically significant difference (mean ± SE: −8.0 ± 0.3%, 95% CI [−8.6, −7.4], P < 0.001; Table 3).

Regarding hemodynamic parameters, no significant between-group differences were noted in the mean HR and MAP at baseline. However, the mean intraoperative HR and MAP were significantly lower in the $MgSO_4$ group than in the control group from 30 to 90 min (P < 0.001) (Figs. 2 and 3).

Postoperative $MgSO_4$ and Δ $MgSO_4$ levels were significantly higher in the $MgSO_4$ group than in the control group (P < 0.001).

No significant differences were noted between the groups in terms of duration of recovery (P = 0.219) (Table 4).

In addition, no significant differences were found between the $MgSO_4$ and the control groups regarding the need for ICU admis-

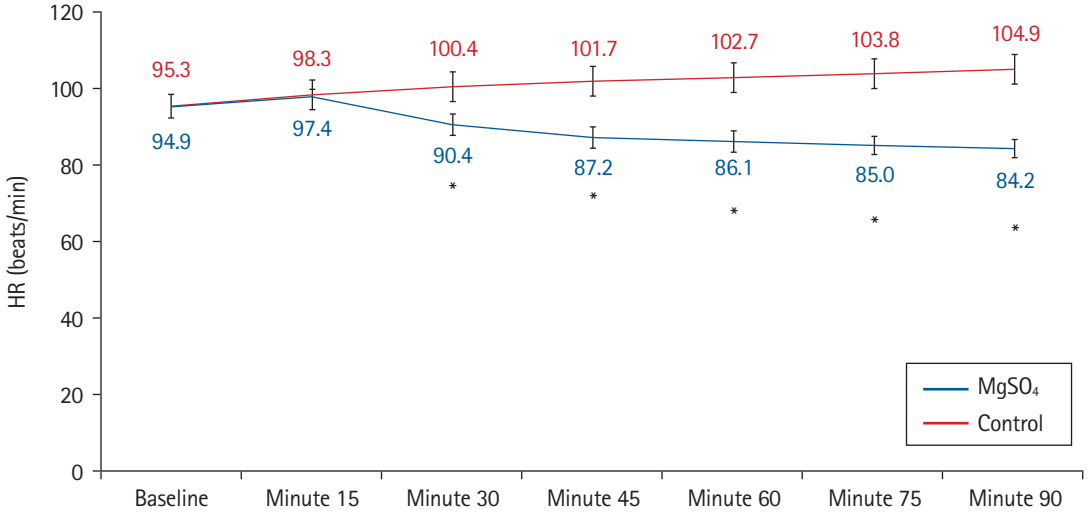

Fig. 2. Comparison of the intraoperative heart rate (HR) between the study groups. Lines are the mean data and error bars are the standard deviation. *P < 0.001 compared to the control group.

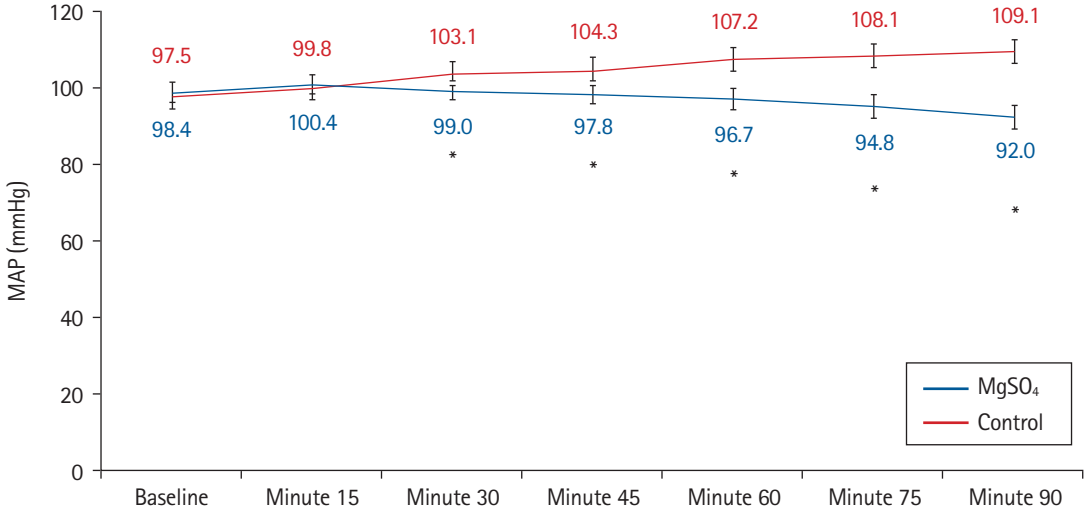

Fig. 3. Comparison of the intraoperative mean arterial pressure (MAP) between the study groups. Lines are the mean data and error bars are the standard deviation. *P < 0.001 compared to the control group.

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Table 4. Comparison of Postoperative Events between the Study Groups

Variable		$MgSO_4$ group (n = 20)	Control group (n = 20)	P value*	Effect size	
					Mean ± SE	95% CI
Postoperative $MgSO_4$ (mg/dl)		2.9 ± 0.3	1.5 ± 0.3	< 0.001†	1.3 ± 0.1	1.1, 1.5
Δ $MgSO_4$ (mg/dl)		1.3 ± 0.1	0.0 ± 0.1	< 0.001†	1.3 ± 0.0	1.2, 1.3
Recovery duration (min)		19.9 ± 1.9	19.1 ± 2.1	0.219	0.8 ± 0.6	−0.5, 2.1
Sedation score	Baseline	1.6 ± 0.5	1.6 ± 0.5	0.757	−0.1 ± 0.2	−0.4, 0.3
	Immediately post-operation	3.2 ± 0.8	3.1 ± 0.7	0.838	0.0 ± 0.2	−0.4, 0.5
	1 h post-operation	2.6 ± 0.5	2.7 ± 0.5	0.531	−0.1 ± 0.2	−0.4, 0.2

Values are presented as mean ± SD. $MgSO_4$ group: magnesium sulfate infusion group, Control group: normal saline infusion group. Δ: delta (time – baseline). Effect size: value of $MgSO_4$ relative to control. *Comparison between the groups. †P value < 0.05; statistically significant.

sion or invasive ventilation postoperatively. Three patients (15%) in the $MgSO_4$ group experienced postoperative hypoxia in the PACU that required ICU admission compared to five patients (25%) in the control group (relative risk [RR] = 0.60, 95% CI [0.17, 2.18], P = 0.695). In addition, two patients (10%) in the $MgSO_4$ group required invasive ventilation compared to four patients (20%) in the control group (RR = 0.50, 95% CI [0.10, 2.43], P = 0.661). No significant differences in sedation scores were found between the two groups at baseline, immediately postoperatively, or 1 h postoperatively (Table 4). Additionally, none of the patients in either group developed any other postoperative complications such as bleeding or leakage.

Discussion

This study demonstrated that infusing $MgSO_4$ intraoperatively has protective effects on arterial oxygenation and lung mechanics in morbidly obese patients with restrictive lung disease undergoing bariatric surgery under general anesthesia. $MgSO_4$ significantly preserved arterial oxygenation by inhibiting a reduction in the intraoperative PaO_2/FiO_2 ratio. Furthermore, $MgSO_4$ was able to maintain dynamic lung compliance (no significant decrease) and dead space (no significant increase) during general anesthesia and mechanical ventilation; however, the clinical relevance of these findings is minimal.

To our knowledge, this is the first clinical study to examine the effects of intraoperative $MgSO_4$ infusion on arterial oxygenation and lung mechanics in morbidly obese patients undergoing bariatric surgery.

Obesity has been shown to cause alterations in lung physiology, including increased respiratory rate, reduced lung volume, diminished chest and lung compliance, increased airway resistance (referred to as decreased lung volume, small airway closure, and airway remodeling by proinflammatory adipokines), and increased oxygen consumption. Furthermore, obesity has been associated with an increased alveolar-arterial oxygen gradient caused by ventilation-perfusion mismatch due to microatelectasis, which worsens in the supine position [24]. Obesity-related increases in adipose tissue mass are associated with enhanced mast cell proliferation. Since mast cells are the primary mediators of allergies, obesity-induced mast cell proliferation may represent a potential pathway for airway illnesses in obese individuals [25].

Patients with morbid obesity are at risk of rapid oxygen desaturation upon general anesthesia induction because the FRC is decreased by approximately 50% compared to preoperative values [4]. The impact of general anesthesia is further intensified by mechanical ventilation and the use of muscle relaxants, which may compromise pulmonary function, lung compliance, and gas exchange owing to the development of atelectasis. Additionally, the patient's position and use of the pneumoperitoneum may lead to further impairment [26,27].

In our study, administering $MgSO_4$ maintained the arterial oxygenation by preventing a reduction in the intraoperative PaO_2/FiO_2 ratio. However, given the small effect size of our study, the clinical significance of these findings is minimal. $MgSO_4$ may preserve intraoperative arterial oxygenation in patients with obesity by promoting both pulmonary vasodilation and bronchodilatation, leading to improved perfusion and ventilation. In general, the therapeutic effects of magnesium may be attributed to its effects as a calcium antagonist [28,29].

$MgSO_4$ can enhance vasodilation by relaxing the tone of the vascular smooth muscles. Moreover, $MgSO_4$ promotes the local synthesis of vasodilator substances such as nitric oxide and prostaglandins (e.g., prostacyclin) [30]. In terms of magnesium-induced bronchodilation, various experimental data suggest that several pathways may be involved, such as the suppression of cholinergic neuromuscular transmission, inhibition of calcium-induced muscle contractions, attenuation of histamine release, reversal of magnesium depletion following β-adrenergic therapy, and enhancement of the effects of β-agonists on adenylyl cyclase

[31–34]. Magnesium also has sedative properties that help people relax and achieve anxiolysis, particularly during acute bronchoconstriction [30].

Additionally, magnesium relaxes rabbit bronchial smooth muscles in a dose-dependent manner when exposed to histamine, bethanechol, or electrical impulses [31]. Similarly, magnesium increases the percentage of the bronchial cross-sectional area in dogs following histamine-elicited bronchoconstriction in vivo and relaxes histamine-induced contractions of guinea pig tracheal strips in vitro [35].

Furthermore, $MgSO_4$ has been found to have bronchodilation effects regardless of baseline serum magnesium levels, even after short periods of drug infusion [27]. These findings could help explain the positive effects of $MgSO_4$ infusions on dynamic compliance and dead space observed in this study. Our results are similar to those of a previous study conducted by Ahmed et al. [20], which showed that an intraoperative infusion of $MgSO_4$ resulted in mild perioperative protective effects against both arterial oxygenation and lung mechanics in patients with moderate COPD following laryngectomy under general anesthesia.

In the current study, the post-infusion serum magnesium level in the Mg group was 2.9 ± 0.3 mg/dl, which is lower than levels associated with magnesium toxicity. Loss of the patellar reflex occurs with plasma levels of 9.6–12 mg/dl, whereas respiratory depression occurs at levels of 12–18 mg/dl [36].

$MgSO_4$ is readily accessible and affordable, with few side effects when administered at recommended doses [37]. It has a rapid onset of action when administered intravenously, which is critical in emergencies. In addition, intravenous $MgSO_4$ is rapidly eliminated from the kidneys. However, this is both a therapeutic opportunity and a challenge. As maximal renal tubular reabsorption of magnesium occurs at normal serum levels and renal clearance increases linearly with higher concentrations, achieving a sustained spasmolytic effect is not easy [38]. The infusion rate, rather than the overall dosage or infusion time, has a greater impact on the maximum serum level throughout treatment. Since it was first described in 1936, the ideal bolus dose of intravenous $MgSO_4$ has not yet been identified. Consequently, a wide dose range of 25–100 mg/kg has been used [38–42].

$MgSO_4$ has been found to have several therapeutic effects in clinical anesthesia, including enhancing postoperative analgesia and reducing the consumption of other anesthetics, opioids, and hypnotics [37]. However, the adverse effects are generally moderate and include intravenous injection pain, residual neuromuscular blockade, and hypotension. Hypermagnesemia is an uncommon complication that usually affects patients with renal failure who are receiving medicines containing magnesium [43]. However, close monitoring is still needed to promptly detect and manage adverse events [44]. No magnesium-related complications were observed in this study.

This study had some limitations. As we enrolled only morbidly obese patients with restrictive lung disease, our findings cannot be generalized to other patient populations. Additionally, this study only included patients who underwent bariatric surgery; therefore, our results should be validated using other surgical procedures. Finally, because intraoperative $MgSO_4$ infusions were not maintained until the end of the procedure, outcomes may vary with longer infusions or greater plasma concentrations.

In conclusion, the intraoperative administration of $MgSO_4$ infusion significantly preserved arterial oxygenation and maintained dynamic lung compliance and dead space in morbidly obese patients; however, the clinical relevance of these findings is minimal. This study failed to adequately reflect the clinical importance of these results.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Marwa M. Mowafi (Conceptualization; Data curation; Investigation; Methodology; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)
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Effects of sevoflurane on metalloproteinase and natural killer group 2, member D (NKG2D) ligand expression and natural killer cell-mediated cytotoxicity in breast cancer: an in vitro study

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Background: We investigated the effects of sevoflurane exposure on the expression of matrix metalloproteinase (MMP), expression and ablation of natural killer group 2, member D (NKG2D) ligands (UL16-binding proteins 1–3 and major histocompatibility complex class I chain-related molecules A/B), and natural killer (NK) cell-mediated cytotoxicity in breast cancer cells.

Methods: Three human breast cancer cell lines (MCF-7, MDA-MB-453, and HCC-70) were incubated with 0 (control), 600 (S6), or 1200 μM (S12) sevoflurane for 4 h. The gene expression of NKG2D ligands and their protein expression on cancer cell surfaces were measured using multiplex polymerase chain reaction (PCR) and flow cytometry, respectively. Protein expression of MMP-1 and -2 and the concentration of soluble NKG2D ligands were analyzed using western blotting and enzyme-linked immunosorbent assays, respectively.

Results: Sevoflurane downregulated the mRNA and protein expression of the NKG2D ligand in a dose-dependent manner in MCF-7, MDA-MB-453, and HCC-70 cells but did not affect the expression of MMP-1 or -2 or the concentration of soluble NKG2D ligands in the MCF-7, MDA-MB-453, and HCC-70 cells. Sevoflurane attenuated NK cell-mediated cancer cell lysis in a dose-dependent manner in MCF-7, MDA-MB-453, and HCC-70 cells ($P = 0.040$, $P = 0.040$, and $P = 0.040$, respectively).

Conclusions: Our results demonstrate that sevoflurane exposure attenuates NK cell-mediated cytotoxicity in breast cancer cells in a dose-dependent manner. This could be attributed to a sevoflurane-induced decrease in the transcription of NKG2D ligands rather than sevoflurane-induced changes in MMP expression and their proteolytic activity.

Keywords: Breast neoplasms; Inhalation anesthetics; Matrix metalloproteinases; Natural killer cells; Sevoflurane; Tumor escape.

Introduction

In 2020, breast cancer surpassed lung cancer as the most common cancer worldwide, accounting for 12.5% of cancer diagnoses [1]. The incidence of breast cancer continues to increase, with a projected increase of > 40% in new cases and > 50% in deaths by 2040 [1]. Approximately 88% of patients with breast cancer undergo at least one anesthetic and surgical treatment within one year of diagnosis [2]. However, surgery and anesthesia are associated with an increased release of inflammatory mediators and angiogenic factors, and cause postoperative immunosuppression, resulting in tumor progression [3].

The natural killer group 2, member D (NKG2D) ligands, UL16-binding proteins (ULBP) 1–3, and major histocompatibility complex class I chain-related molecules (MIC) A/B, which are expressed on the surface of cancer cells, bind to active receptors on natural killer cells (NK cells), transmitting signals and allowing NK cells to recognize and eliminate cancer cells [4]. A reduction in the expression of NKG2D ligands can impair the cytotoxicity of NK cells against cancer cells, leading to immune evasion and disruption of the cancer immunosurveillance system [5].

Matrix metalloproteinases (MMPs) are Zn^{2+}-dependent endopeptidases that play a critical role in tumor progression by promoting extracellular matrix and basement membrane degradation, leading to cell detachment and migration [5,6]. MMPs also promote neovascularization and contribute to tumor angiogenesis [5,6]. Moreover, recent cancer immunological studies have demonstrated that MMPs cleave and remove NKG2D ligands [5–7]. MMP-induced shedding of NKG2D ligands confers several advantages to cancer cells for immune evasion [8,9]. First, it reduces the density of NKG2D ligands on the surface of cancer cells, thereby impairing their susceptibility to NK cells [8,9]. Moreover, the cleaved ligands (soluble NKG2D ligands) retain their ability to bind to the NKG2D receptors on NK cells [8,9]. This cleaved ligand-receptor engagement not only hinders the activation signaling of the receptor, but also triggers the internalization and downmodulation of the NKG2D receptor on NK cells [8,9].

The modulation of surgery-related factors in clinical practice remains challenging and requires an enhanced understanding of the effects of anesthesia-related factors on cancer recurrence and survival rates. Therefore, elucidating the effects of anesthetics on the breast cancer microenvironment is essential for optimal anesthesia management and an improvement in postoperative outcomes.

In this study, we investigated the effects of sevoflurane, a common general anesthetic, on MMP expression and NKG2D-mediated NK cell cytotoxicity in breast cancer cells. We evaluated the effects of sevoflurane on MMP expression, NKG2D ligand expression and ablation, and NK cell-mediated cytotoxicity in breast cancer cells.

Materials and Methods

Cell lines and reagents

This study was conducted using the following three breast cancer cell lines: estrogen receptor (ER)- and progesterone receptor (PR)-positive human breast cancer cell line MCF-7 (Korean Cell Line Bank, Korea), human epidermal growth factor receptor 2 (HER2)-positive human breast cancer cell line MDA-MB-453 (Korean Cell Line Bank), and triple-negative human breast cancer cell line HCC-70 (Korean Cell Line Bank) [10]. All cell lines were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum and 1% penicillin (Welgene, Korea). Because sevoflurane is a strong organic solvent capable of interacting with plastic materials to produce impurities [11], breast cancer cells were cultured in poly-L-lysine-coated (Sigma-Aldrich, USA) glass culture dishes.

The human NK cell line, NK92-MI (ATCC, USA), was maintained in an α-minimum essential medium containing fetal bovine serum (12.5%), horse serum (12.5%), 2 mercaptoethanol (0.1 mM), and L-glutamine (2 mM). All cell lines were cultured according to their specifications and incubated at 37°C in humidified air containing 5% CO_2.

Sevoflurane treatment

As previously described [12–14], 100 μl sevoflurane (Sevoprane; Ilsung, Korea) was diluted in 10 ml RPMI-1640 medium and stirred for a half-hour in an airtight, amber-colored glass bottle. The concentration of sevoflurane was determined using the preliminary data obtained from our gas chromatography-mass spectrometry analysis (GCMS-QP2010 Plus; Shimadzu, Japan) as (mean [SD]): 3.92 (1.26) mM. The sevoflurane stock was serially diluted to 1200 and 600 μM (S12 and S6, respectively) immediately before the experiments. Kharasch et al. [15] simultaneously measured the end-tidal sevoflurane concentration and plasma concentration of sevoflurane during general anesthesia and revealed that the average peak plasma concentration of sevoflurane reached 772 μM at an end-tidal sevoflurane concentration of 2.7% (equivalent to 1.3 minimum alveolar concentration). Consequently, we assumed clinically relevant concentrations of sevoflurane at 600 μM during general anesthesia. Furthermore, to investigate the dose-response relationship, we administered an additional dose of sevoflurane at a concentration

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of 1200 μM, which was higher than the recommended dose. The corresponding concentration of distilled water in the RPMI 1640 media were used as controls (0 μM).

The MCF-7, MDA-MB-453, and HCC-70 cells were then exposed to sevoflurane for 4 h. To account for evaporation-induced concentration reduction, both the sevoflurane and control group solutions were replaced every hour (Fig. 1) [13,14]. Previous studies [12,13] have shown that despite the volatility of sevoflurane, the concentration of the sevoflurane solution dissolved in cell culture media remains stable, with a < 10% loss over a one-hour period.

mRNA expression analysis was performed 18 h after treatment completion, while the other experiments (cell viability test, flow cytometry assay for surface expression of NKG2D ligands, western blotting analysis, enzyme-linked immunosorbent assay [ELISA] for soluble NKG2D ligands, and flow cytometry assay for NK cell-mediated cytotoxicity) were performed 24 h after treatment completion (Fig. 1).

Cell viability test

The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay is based on the principle that mitochondrial activity in living cells converts MTT into formazan crystals. These crystals are dissolved following the addition of dimethyl sulfoxide (DMSO) and detected spectrophotometrically at 540 nm, with the absorbance directly proportional to cell viability [16]. As previously described [14], the MCF-7, MDA-MB-453, and HCC-70 cells were plated in 96-well plates (1×10^4 cells/well) and incubated with the control or S12 solution for 4 h. Twenty-four hours later, the cells were incubated with the MTT solution (Sigma-Aldrich) for 4 h. The supernatant was discarded and the formazan crystals were dissolved using DMSO. The absorbance at 540 nm was determined using a microplate spectrophotometer (μQuant; Bio Tek, USA).

mRNA expression analysis of NKG2D ligands

The mRNA expression analysis method used has been described previously [14]. Briefly, after a 4-h treatment and an additional 18-h incubation period, cancer cells were harvested (Fig. 1). The total RNA was extracted from the cells using a RNeasy® Mini kit (Qiagen GmbH, Germany). Reverse transcription polymerase chain reaction (RTPCR) and multiplex PCR were performed. For denaturation, 3 μg extracted total RNA and 100 pmol random primers (Takara Shuzo, Japan) were incubated at 65°C for 5 min and chilled at 4°C for 4 min. Next, 6 μl of the 5x reaction buffer, 4 μl deoxynucleotide triphosphate (10 mM; Promega Co., USA), and 1.2 μl M-MLV RT (Promega Co.) were added and incubated at 37°C for 60 minutes. Multiplex PCR was performed using a QIAGEN® Multiplex PCR kit (Qiagen GmbH). The primer sets used to evaluate NKG2D gene expression were as follows: 1) MICA: ribosomal protein L19 (RPL19), MICA, and β-actin genes and 2) MICB and ULBP 1–3: RPL19, MICB, ULBP1–3, and β-actin genes. The primer sequences are listed in Table 1. All the experiments were performed according to the manufacturer's instructions. PCR products were quantified using a microchip electrophoresis system MCE®-202MultiNA (Shimadzu, Japan). For normalization, the mRNA band intensity of

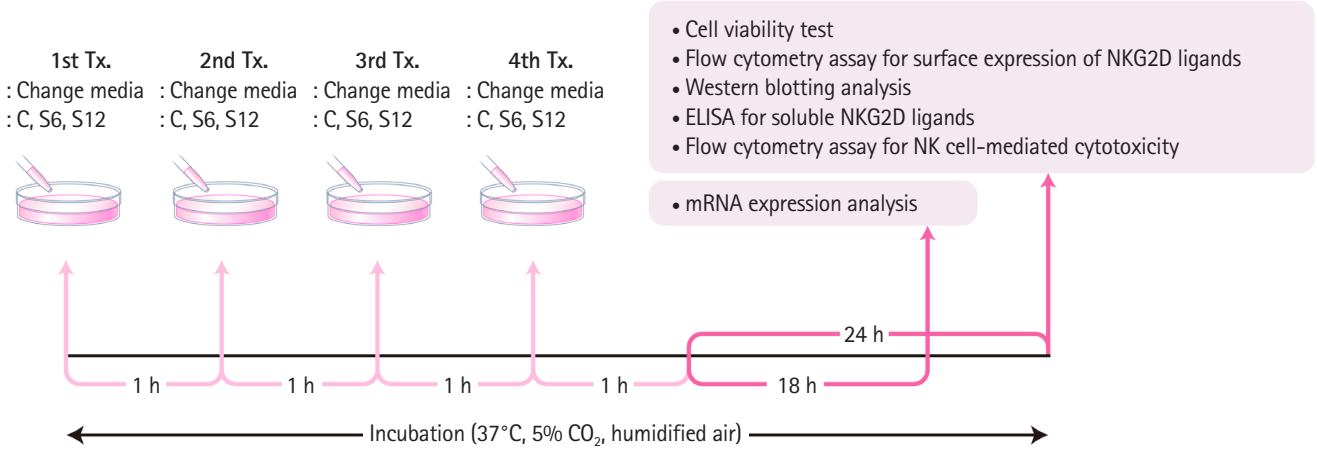

Fig. 1. Experimental protocol used in the study. Treatment (1200 [S12], 600 [S6], and 0 [control, C] μM) was administered for 4 h, and each sevoflurane and control group solution was replaced on an hourly basis. mRNA expression analysis was performed 18 h after completion of the 4-h treatment. The other tests were performed 24 h after the 4-h treatment.

each NKG2D ligand was divided by that of the β-actin. To assess relative gene expression ratios, the normalized mRNA band intensity of the treated samples was divided by that of the controls.

Flow cytometry assay for surface expression of NKG2D ligands

The flow cytometry assay for the surface expression of NKG2D ligands was performed using the method described in our previous study [14]. Briefly, after a 4-h treatment and an additional 24-h incubation period (Fig. 1), the cells were harvested and incubated with 10 μg/ml mouse anti-MICA/B and ULBP1–3 or the corresponding isotype controls (anti-IgG2a or anti-IgG2b; R&D Systems, USA). Samples were then incubated with goat anti-mouse phycoerythrin (PE)-conjugated antibodies (BD Biosciences, USA). The mean fluorescence intensity (MFI) was measured using a FACSCanto II flow cytometer (BD Biosciences) and quantified using FlowJo (version 10.6.1; TreeStar, USA). The MFIs of the treated samples were divided by those of the controls to assess the relative expression ratios.

Western blot analysis for determining protein expression of MMPs

After a 4-h treatment and an additional 24-h incubation period (Fig. 1), western blot analysis was performed to evaluate MMP-1 and -2 expression. The cells were washed three times with cold phosphate-buffered saline and lysed in a PRO-PREP protein extraction solution (Intron, Korea). Equal amounts of cell extracts were resolved by 4%–20% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and analyzed by western blotting. The separated proteins were transferred onto polyvinylidene difluoride membranes (Millipore, USA). The membranes were then blocked with 3% BSA in Tris-buffered saline containing 0.1% Tween 20 at room temperature. The proteins of interest were detected using primary antibodies (MMP-1 and -2; Cell Signalling, USA) and horseradish peroxidase-conjugated secondary antibodies (Enzo Life Sciences, USA) according to the manufacturer's instructions, and a chemiluminescence imaging system (AE-9150 Ez-capture II; Atto, Japan) was used to analyze the results. Each blot was probed with anti-β-actin antibodies (Sigma-Aldrich). Band intensity was quantified using ImageJ software (version 1.53; National Institutes of Health, USA). Protein expression in the treated cells was divided by that in the control cells to calculate relative protein expression ratios.

Enzyme-linked immunosorbent assay (ELISA) for soluble NKG2D ligands

Breast cancer cells (4 × 106 cells) were plated on 60-mm glass culture dishes. After a 4-h treatment and an additional 24-h incubation period (Fig. 1), cell culture supernatants were centrifuged at 5000 rpm for 5 min at 4°C, and aliquots were stored at −80°C until further use. The levels of soluble NKG2D ligands (MICA for MCF-7 and MDA-MB-453; MICB for HCC-70) in the cell culture supernatant were measured using ELISA kits (MICA Human ELISA kit, Invitrogen, USA; Human MICB ELISA kit, MyBioSource, USA) following the manufacturer's protocol. The absor-

Table 1. List of Primers Used in Multiplex RTPCR

Name	Polarity	Sequence (5' → 3')	Amplicon length (bp)
MICA	Sense	TTGAGCCGCTGAGAGGGTGGC	460
	Anti-sense	GGGAGAGGAAGAGCTCCCCATC	
MICB	Sense	GCCCCCTGACCCCTTGTTCC	358
	Anti-sense	GGGCTGGTCAACTTGGCGAAA	
ULBP1	Sense	TGGCTGGTCCCGGGCAGGAT	266
	Anti-sense	GAATGTCAAGCAGTTGCCCTTTAAGGAAA	
ULBP2	Sense	TCAAACTCGCCCTTCTGTCTGGC	194
	Anti-sense	GCAGGAATTCCATCAGGTAGCACCA	
ULBP3	Sense	AGGTCTTATCTATGGGTCACCTAGAAG	132
	Anti-sense	TGAAATCCTCCAGCTCAGTGTCAGC	
RPL19	Sense	ATGCTCAGGCTTCAGAAGAGGCTCG	550
	Anti-sense	TGATGATCTCCTCCTTCTTGGCCTG	
β-actin	Sense	TCCATCCTGGCCTCGCTGTC	93
	Anti-sense	GCATTTGCGGTGGACGATGG	

RTPCR: reverse transcriptase polymerase chain reaction, MICA/B: MHC class I chain-related molecules A/B, ULBP: UL16-binding proteins, RPL19: ribosomal protein L19.

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bance at 450 nm was measured using a microplate spectrophotometer (Synergy H1; BioTek, USA). The samples were loaded in duplicate, and the mean soluble NKG2D ligand values were used for analysis.

Flow cytometry assay for NK cell-mediated cytotoxicity

After a 4-h treatment and an additional 24-h incubation period (Fig. 1), target cancer cells (MCF-7, MDA-MB-453, and HCC-70) were stained with carboxyfluorescein diacetate succinimidyl ester (CFSE; CellTrace™; Invitrogen) and co-cultured with NK92-MI cells, effector cells, for 4 h. With cellular cytotoxicity assays, optimizing the effector-to-target cell (E:T) ratio is crucial for maximizing and distinguishing differences in cytotoxicity among treatment groups. Typically, higher E:T ratios result in enhanced NK cell cytotoxicity because an increased number of effector cells relative to target cells leads to greater cytotoxicity [17]. The recommended E:T ratio for flow cytometry cytotoxicity assays is ≤ 10:1 [18]. As previously reported [14], we determined the E:T ratio to be between 1:1 (e.g., E:T = $1 \times 10^5 : 1 \times 10^5$) and 10:1 (e.g., E:T = $1 \times 10^6 : 1 \times 10^5$), with 10:1 as the optimal ratio. Co-cultured cells were labelled with 1 μg/ml propidium iodide (PI; Invitrogen). A FACSCanto™ II flow cytometer and BD FACSDiva™ Software (BD Biosciences) were used. The percentage of NK cell-mediated lysis (%) was calculated using the following equation:

$$\frac{Q2}{Q2 + Q3} \times 100$$

where Q2 represents CFSE-positive and PI-positive cells and Q3 represents CFSE-positive and PI-negative cells.

Statistical analysis

MedCalc® (version 20; MedCalc Ltd., Belgium) and IBM SPSS Statistics (version 25; IBM Corp., USA) were used for statistical analyses. Variables are presented as medians with the first and third quartiles (Q1, Q3). For comparisons between groups, Mann-Whitney *U* tests or Kruskal-Wallis tests were performed. If the Kruskal-Wallis test was significant, post-hoc comparisons using the Conover method were conducted.

Our trial consisted of a zero-dose control group (C) and two sevoflurane treatment groups (S6 and S12) that received increasing doses of sevoflurane in the following order: C, S6, S12. As a secondary outcome, the dose-response relationship was evaluated using the Jonckheere-Terpstra trend test. Statistical significance was set at $P < 0.05$.

Results

Effect of sevoflurane on cell viability assessed by MTT assay

Sevoflurane was not found to affect the viability of MCF-7, MDA-MB-453, or HCC-70 cells. The relative cell viabilities (%) related to the controls measured by MTT assay were as follows (median [Q1, Q3]): MCF-7 at S12: 100.2 (92.4, 118.9), P = 1.000; MDA-MB-453 at S12: 101.4 (96.2, 109.0), P = 1.000; and HCC-70 at S12: 89.4 (87.3, 107.0), P = 0.305 (n = 6 per group).

Effect of sevoflurane on the mRNA expression of NKG2D ligands

The results of sevoflurane exposure on the mRNA expression of NKG2D ligands are summarized in Fig. 2 (n = 6 per group). In MCF-7, MDA-MB-453, and HCC-70 cell lines, mRNA expression of MICA, MICB, ULBP2, and ULBP3 was observed, but the expression of ULBP1 was not observed.

In MCF-7 cells, the relative mRNA expression ratios of MICB at S6 and S12 were lower than those in the controls (Kruskal-Wallis test: P = 0.013). In MDA-MB-453 cells, the relative mRNA expression ratios of MICA at S6 and S12 were lower than those in the controls (Kruskal-Wallis test: P = 0.013) and the relative surface expression ratio of ULBP3 was downregulated at S12 compared with the controls (Kruskal-Wallis test: P = 0.044). In HCC-70 cells, the relative mRNA expression ratios of ULBP2 and ULBP3 at S6 and S12 were lower than those in the controls (Kruskal-Wallis test: P = 0.002 and P = 0.003, respectively).

The secondary outcome results showed a dose-response relationship in MCF-7 cells, demonstrating significantly lower relative mRNA expression levels of MICA, MICB, ULBP2, and ULBP3 in response to increasing concentrations of sevoflurane (Jonckheere-Terpstra trend test: P = 0.015, P = 0.008, P = 0.036, and P = 0.043, respectively). Similarly, sevoflurane downregulated the mRNA expression of MICA and ULBP3 in MDA-MB-453 cells in a dose-dependent manner (Jonckheere-Terpstra trend test: P = 0.002 and P = 0.029, respectively). Likewise, sevoflurane downregulated the mRNA expression of MICA, MICB, ULBP2, and ULBP3 in HCC-70 cells in a dose-dependent manner (Jonckheere-Terpstra trend test: P = 0.043, P = 0.043, P = 0.006, and P = 0.012, respectively).

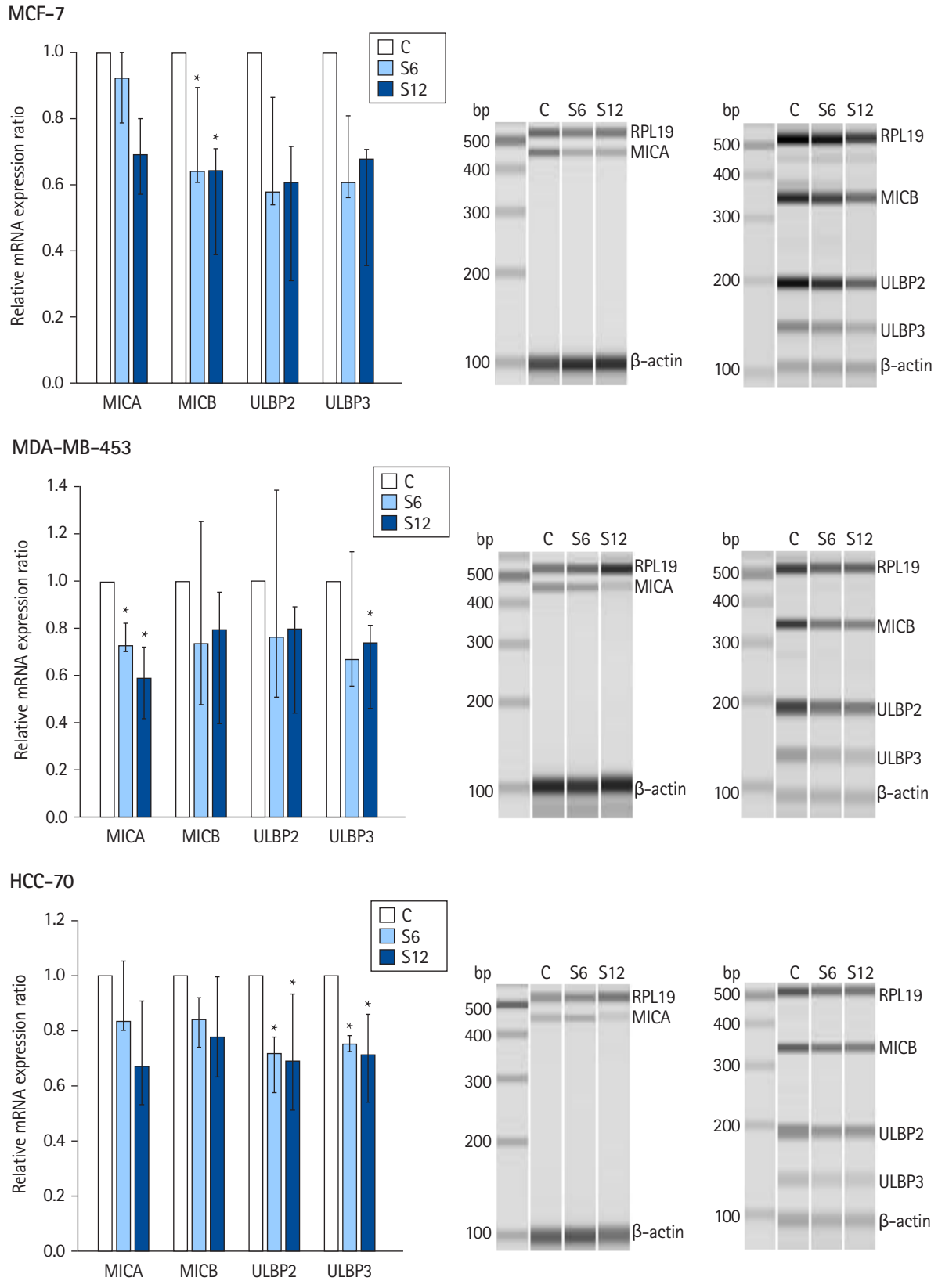

Fig. 2. Effect of sevoflurane on the mRNA expression of NKG2D ligands. Results were analyzed using Kruskal-Wallis tests with post-hoc Conover comparisons. Variables are presented as the median with the first and third quartiles (n = 6 per group). C: control group, S6: sevoflurane 600 μM group, S12: sevoflurane 1200 μM group, ULBP: UL16-binding proteins, MICA/B: major histocompatibility complex class I chain-related molecules A/B, RPL19: ribosomal protein L19. *P < 0.05 compared to C.

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Effect of sevoflurane on surface expressions of NKG2D ligands assessed by flow cytometry

Fig. 3 summarizes the results of the flow cytometry analysis of NKG2D ligand surface expression (n = 6 per group). Consistent with mRNA expression, ULBP1 was rarely expressed on the surface of the MCF-7, MDA-MB-453, and HCC-70 cell lines.

In MCF-7 cells, MICA and ULBP2 were predominantly ex-

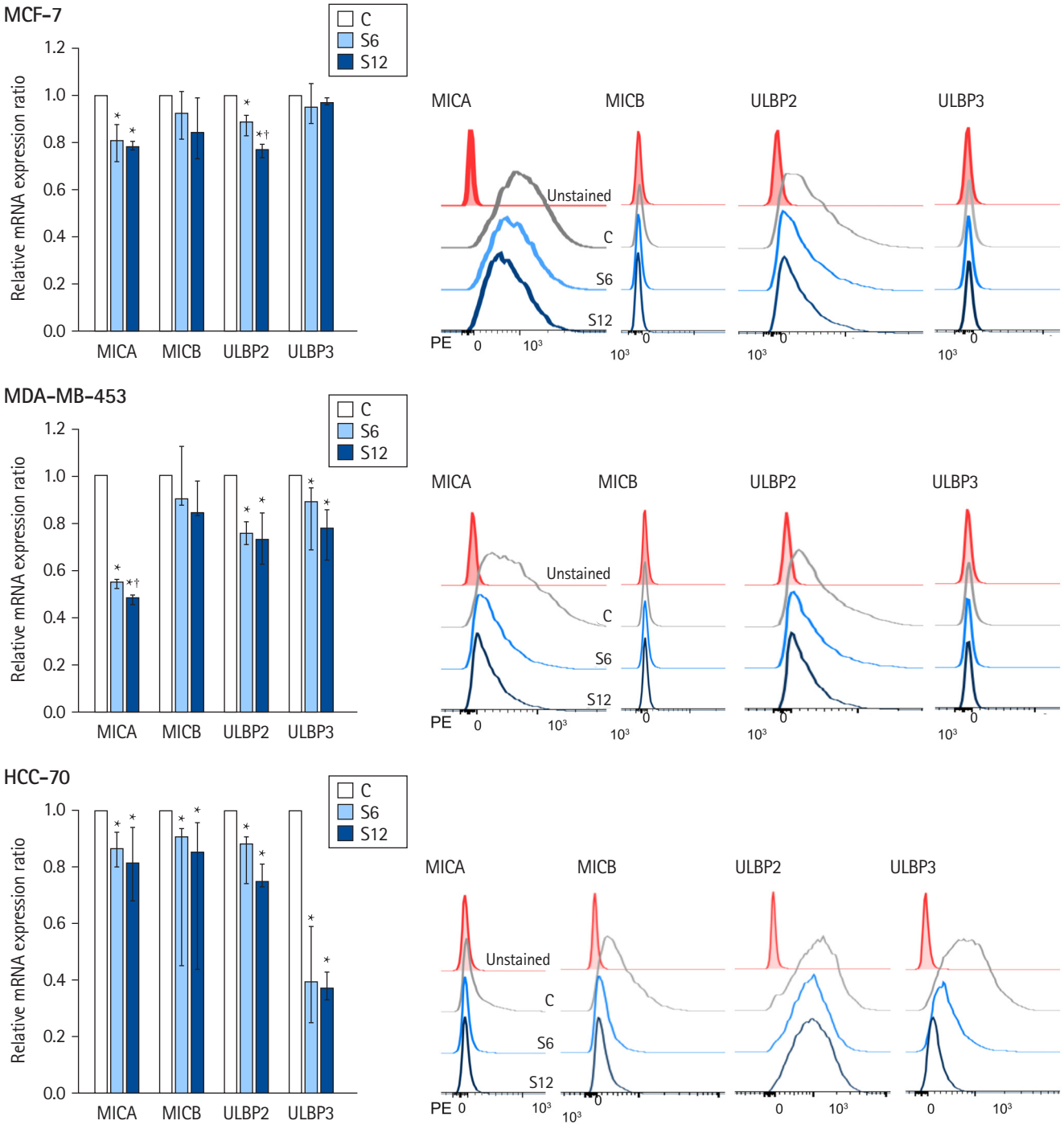

Fig. 3. Effect of sevoflurane on surface expressions of NKG2D ligands assessed by flow cytometry. Results were analyzed using Kruskal-Wallis tests with post-hoc Conover comparisons. Variables are presented as the median with the first and third quartiles (n = 6 per group). C: control group, S6: sevoflurane 600 μM group, S12: sevoflurane 1200 μM group, ULBP: UL16-binding proteins, MICA/B: major histocompatibility complex class I chain-related molecules A/B, PE: phycoerythrin. * and †P < 0.05, compared with C and S6, respectively.

pressed; the relative surface expression ratios of MICA and ULBP2 at S6 and S12 were downregulated compared to those in the controls (Kruskal-Wallis test: P = 0.002 and P ≤ 0.001, respectively).

MDA-MB-453 cells predominantly exhibited surface expression of MICA and ULBP2. The relative surface expression ratios of MICA, ULBP2, and ULBP3 at S6 and S12 were lower than those in the controls (Kruskal-Wallis test: P < 0.001, P = 0.003, and P = 0.004, respectively).

In HCC-70 cells, MICB, ULBP2, and ULBP3 were predominantly expressed. The relative surface expression ratios of MICA, MICB, ULBP2, and ULBP3 at S6 and S12 were downregulated compared with those in the controls (Kruskal-Wallis test: P = 0.002, P = 0.017, P = 0.002, and P = 0.013, respectively).

In the dose-response analysis, we observed significantly lower relative surface expression ratios of MICA, MICB, and ULBP2 in MCF-7 cells with increasing concentrations of sevoflurane (Jonckheere-Terpstra trend test: P < 0.001, P = 0.024, and P < 0.001, respectively). Similarly, sevoflurane decreased the relative surface expression ratios of MICA, ULBP2, and ULBP3 in MDA-MB-453 cells in a dose-dependent manner (Jonckheere-Terpstra trend test: P < 0.001, P = 0.002, and P = 0.001, respectively). Likewise, sevoflurane downregulated the relative surface expression ratios of MICA, MICB, ULBP2, and ULBP3 in HCC-70 cells in a dose-dependent manner (Jonckheere-Terpstra trend test: P = 0.001, P = 0.010, P < 0.001, and P = 0.029, respectively).

Effect of sevoflurane on protein expression of MMP assessed by western blot analysis

Western blot analysis revealed no changes in the protein expression of MMP-1 and -2 between the control and sevoflurane treatment groups in MCF-7, MDA-MB-453, and HCC-70 cells (Fig. 4A; n = 6 per group).

In MCF-7 cells, the median (Q1, Q3) of the relative protein expression ratio of MMP-1 was as follows: controls, 1.7 (0.9, 2.4); S6, 1.6 (0.8, 2.5); and S12, 1.5 (0.7, 2.3). P values for the Kruskal-Wallis and Jonckheere-Terpstra trend tests were 0.519 and 0.258, respectively. The median (Q1, Q3) of the relative protein expression ratio of MMP-2 was as follows: controls, 1.3 (0.8, 2.4); S6, 1.3 (1.1, 2.0); and S12, 1.3 (0.8, 2.1). P values for the Kruskal-Wallis and Jonckheere-Terpstra trend tests were 0.854 and 0.686, respectively.

In MDA-MB-453 cells, the median (Q1, Q3) of the relative protein expression ratio of MMP-1 was as follows: controls, 1.3 (0.9, 1.5); S6, 2.0 (0.9, 5.3); and S12, 1.5 (0.7, 3.9). P-values for the Kruskal-Wallis and Jonckheere-Terpstra trend tests were 0.653 and 0.628, respectively. The median (Q1, Q3) of the relative protein expression ratio of MMP-2 was as follows: controls, 0.9 (0.5, 1.1); S6, 0.8 (0.7, 0.9); and S12, 0.8 (0.8, 1.3). P values for the Kruskal-Wallis and Jonckheere-Terpstra trend tests were 0.778 and 0.746, respectively.

In HCC-70 cells, the median (Q1, Q3) of the relative protein expression ratio of MMP-1 was as follows: controls, 1.7 (1.0, 2.3); S6, 1.2 (0.8, 1.7); and S12, 1.4 (0.8, 2.1). P-values for the Kruskal-Wallis and Jonckheere-Terpstra trend tests were 0.423 and 0.293, respectively. The median (Q1, Q3) of the relative protein expression ratio of MMP-2 was as follows: controls, 0.8 (0.4, 1.0); S6, 0.7 (0.4, 1.0); and S12, 0.9 (0.4, 1.0). P values for the Kruskal-Wallis and Jonckheere-Terpstra trend tests were 0.911 and 0.808, respectively.

Sevoflurane did not affect the soluble NKG2D ligand concentration assessed by ELISA

According to the ELISA results, no significant changes were detected in the levels of soluble NKG2D ligands between the control and sevoflurane-treated groups in MCF-7, MDA-MB-453, or HCC-70 cells (Fig. 4B, n = 6 per group).

According to the Jonckheere-Terpstra test results, no dose-response relationship was identified. P values for the MCF-7, MDA-MB-453, and HCC-70 cells were 0.467, 0.125, and 0.686, respectively.

Effect of sevoflurane on NK cell-mediated cytotoxicity assessed by flow cytometry

The flow cytometry results are shown in Fig. 5 (n = 4 per group). In all cell lines, NK cell-mediated cytotoxicity at S6 and S12 was lower than that in the controls. Compared with the controls, the P values were as follows: MCF-7 at S6: 0.005 and MCF-7 at S12: 0.005; MDA-MB-453 at S6: 0.005 and MDA-MB-453 at S12: 0.005; and HCC-70 at S6: 0.005 and HCC-70 at S12: 0.005 (Fig. 5; effect cells:target cells = 10:1, n = 4 per group).

Analysis of the secondary outcomes using the Jonckheere-Terpstra trend test revealed that sevoflurane reduced NK cell-mediated cytotoxicity in MCF-7, MDA-MB-453, and HCC-70 cells in a dose-dependent manner (effector cells:target cells = 10:1; P = 0.040, P = 0.040, and P = 0.040, respectively).

Discussion

In this study, we demonstrated that sevoflurane downregulated the mRNA and protein expression of NKG2D ligands in human breast cancer cell lines in a dose-dependent manner. However,

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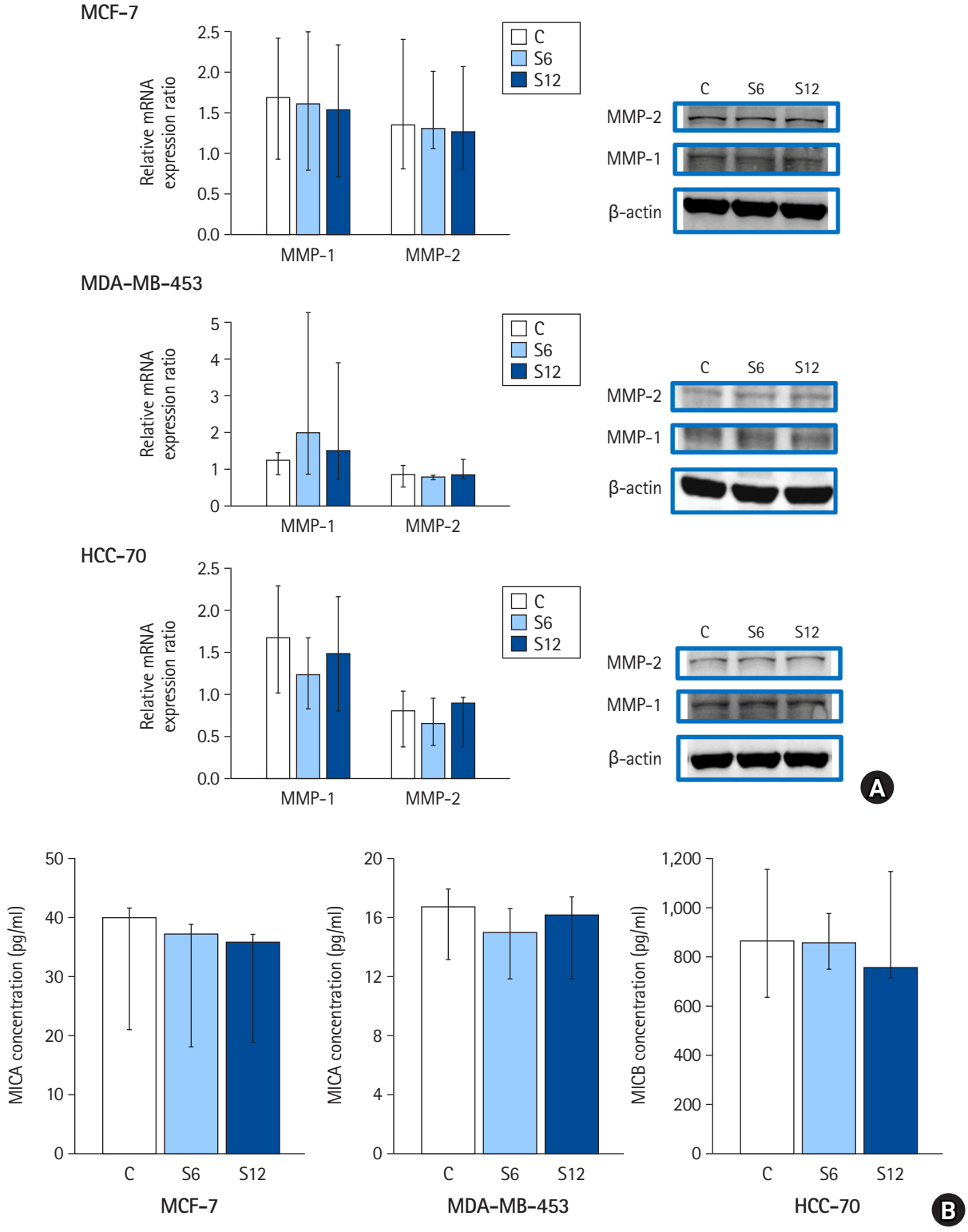

Fig. 4. Effect of sevoflurane on MMP expression and concentration of soluble NKG2D ligands. Variables are presented as medians with the first and third quartiles (n = 6 per group). (A) Western blot analysis was performed to evaluate MMP-1 and -2 expression (Supplementary Fig. 1). The protein expression levels of MMP-1 and -2 between the control and sevoflurane-treated groups in MCF-7, MDA-MB-453, and HCC-70 cells remained unchanged. (B) Enzyme-linked immunosorbent assay (ELISA) tests were performed to evaluate the concentration of soluble NKG2D ligands. No differences in the levels of soluble NKG2D ligands were observed between the control and sevoflurane treatment groups in the MCF-7, MDA-MB-453, and HCC-70 cells. MMP: matrix metalloproteinase, MICA/B: major histocompatibility complex class I chain-related molecules (MIC) A/B, C: control group, S6: sevoflurane 600 μM group, S12: sevoflurane 1200 μM group.

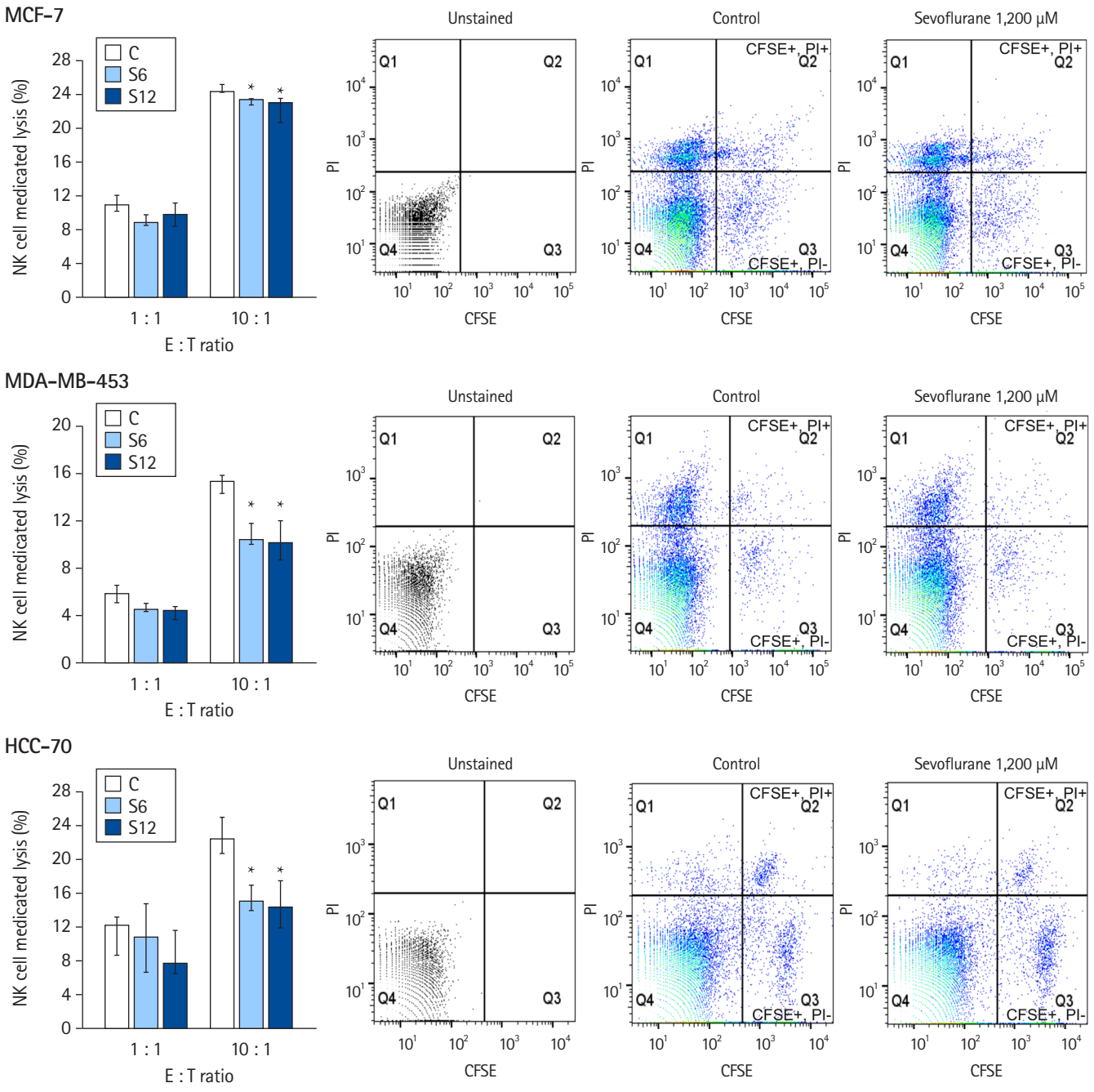

Fig. 5. Effect of sevoflurane on NK cell-mediated cytotoxicity assessed by flow cytometry. Results were analyzed using Kruskal-Wallis tests with post-hoc Conover comparisons. Variables are presented as the median with the first and third quartiles (n = 4 per group). Target cancer cells (T; MCF-7, MDA-MB-453, and HCC-70) were stained with carboxyfluorescein diacetate succinimidyl ester (CFSE) and co-cultured with NK92-MI cells (effector cells [E]) at a 1:1 ratio (e.g., E:T = $1 \times 10^5 : 1 \times 10^5$) or 10:1 (e.g., E:T = $1 \times 10^6 : 1 \times 10^5$). PI: propidium iodide, C: control group, S6: sevoflurane 600 μM group, S12: sevoflurane 1200 μM group. *P < 0.05 compared to C.

sevoflurane was not found to affect the expression of MMP-1 and -2 or the concentration of proteolytically cleaved soluble NKG2D ligands. Furthermore, sevoflurane attenuated NK-cell-mediated cancer cell lysis in a dose-dependent manner.

The association between anesthetics and cancer recurrence was first reported in the 2000s. Since then, several preclinical and clinical studies have been conducted to identify the potential effects of anesthetics and anesthesia methods on breast cancer prognosis [19–21]. Although preclinical trials have suggested potential associations between anesthetic agents and breast cancer invasion and

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metastasis, the results of clinical research comparing these effects remain inconclusive [19]. A recent meta-analysis, in a subgroup analysis of breast cancer based on a prospective and three retrospective clinical studies, reported that recurrence-free survival and overall survival rates of breast cancers did not improve when total intravenous anesthesia was used compared with inhalation anesthesia (hazard ratio [HR], 95% CI of recurrence-free survival: 0.83 [0.59, 1.15]; overall survival: 1.12 [0.90, 1.39]) [22]. Sessler et al. [23] conducted a multicenter randomized controlled trial and demonstrated that recurrence-free survival did not differ between sevoflurane-based general and regional anesthesia with propofol (adjusted HR, 95% CI: 0.97 [0.74, 1.28]).

Our results demonstrate that sevoflurane suppresses NK cell-mediated cancer cell lysis in a dose-dependent manner. Consistent with our results, previous studies have demonstrated a potential association between sevoflurane exposure and the inhibition of NK cell activity and have suggested various underlying mechanisms in breast cancer patients [24,25]. In a pilot clinical trial conducted on ten breast cancer patients, sevoflurane-based general anesthesia reduced the expression of the NK cell-activating receptor (CD16) and their cytokines (interleukin [IL]-1β and IL-10) and decreased NK cell-mediated cytotoxicity [24]. Similarly, in another randomized controlled trial that included 50 participants, NK cell-mediated cytotoxicity decreased after breast cancer resection under sevoflurane-based anesthesia with fentanyl analgesia [25].

In our previous study on a non-small cell lung cancer cell line, sevoflurane administered at an anesthetic dose decreased NKG2D ligand expression and NK cell-mediated cytotoxicity. This effect was attributed to the suppression of NKG2D ligand transcription and an increase in MMP expression [14]. However, the present study on breast cancer cell lines suggests a different mechanism for the reduction of NK cell-mediated cytotoxicity by sevoflurane. We propose that sevoflurane directly inhibits the transcription of NKG2D ligands rather than the NKG2D ligand shedding induced by increased MMP expression.

Previous studies examining the effects of sevoflurane on MMP expression in breast cancer have yielded conflicting results [26,27]. Deegan et al. [26] reported that, following primary breast cancer surgery, sevoflurane with opioid anesthesia increased the serum levels of MMP-3 and MMP-9, but not MMP-1, compared to propofol with a paravertebral block. In contrast, Galos et al. [27] demonstrated no difference in the serum levels of MMP-3 and MMP-9 before or after sevoflurane-based anesthesia in patients with breast cancer. These discrepancies could be attributed to the heterogeneity in cancer subtypes, patient characteristics, and anesthetic exposure regimens. However, only a limited number of studies have evaluated the effects of anesthetic agents on NK cell ligand expression in breast cancer.

Our study had a few limitations. First, as this was an *in vitro* study, our results are not directly applicable to animals or humans. Second, the present study was not designed to elucidate the molecular mechanism by which sevoflurane affects the expression of NKG2D ligands and MMPs; therefore, further studies are warranted to understand the detailed mechanism. Third, sevoflurane was the only anesthetic agent used in this study. Consequently, whether our results represent a universal phenomenon associated with higher concentrations of anesthetics or are specific to sevoflurane remains unknown. For a comprehensive understanding of our findings, additional research using other anesthetic agents such as propofol is necessary.

In summary, sevoflurane was found to attenuate NK cell-mediated cancer cell lysis in a dose-dependent manner, which could be attributed to the sevoflurane-induced decrease in the transcription of NKG2D ligands rather than sevoflurane-induced changes in MMP expression and their proteolytic activity. Further research is essential to elucidate the effects of sevoflurane on immune escape and immunosurveillance in breast cancer.

Funding

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Hyae Jin Kim (Conceptualization; Investigation; Writing – original draft; Writing – review & editing)
Soeun Jeon (Conceptualization; Data curation; Funding acquisition; Investigation; Visualization; Writing – original draft; Writing – review & editing)
Hyeon Jeong Lee (Conceptualization; Formal analysis; Methodology; Supervision; Writing – review & editing)
Jaeho Bae (Conceptualization; Investigation; Methodology; Su-

pervision; Validation; Writing – review & editing)
Hyun-Su Ri (Formal analysis; Investigation; Writing – original draft)
Jeong-Min Hong (Investigation; Methodology; Visualization; Writing – review & editing)
Sung In Paek (Formal analysis; Investigation; Writing – original draft)
Seul Ki Kwon (Methodology; Visualization)
Jae-Rin Kim (Investigation; Methodology)
Seungbin Park (Investigation; Methodology; Validation)
Eun-Jung Yun (Investigation; Visualization)

Supplementary Material

Supplementary Fig. 1. Effect of sevoflurane on MMP expression (uncropped image).

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Breathing circuit leak – an unexpected finding

Owing to the decreased risk of pulmonary cross-contamination associated with disposable breathing circuits, their use is increasing. However, these circuits may be a source of airway obstruction or leakage [1]. Leaks in the breathing circuit occur in more than 50% of tested circuits, and most are resolved during routine machine checks [2]. We report a case of breathing circuit leakage due to an unintentional human error that occurred intraoperatively. Written informed consent for publication of this report was obtained from the patient.

A female patient aged 17 years and weighing 40 kg was scheduled for a left frontal craniotomy and left frontal bleed evacuation. She had a Glasgow Coma Score of 15 and no motor deficits. The patient was known to have atrial and ventricular septal defects with tricuspid atresia, and her oxygen saturation was 88 percent on room air. Before the start of the case, the anesthesia machine (Dräger Primus; Drägerwerk AG & Co, Germany) passed a routine self-test as per manufacturer's recommendation, with no errors detected. No leaks or defects were observed in the newly attached disposable anesthesia breathing circuit. After anesthesia induction, the orotracheal intubation was done with a 7.0-mm inner diameter endotracheal tube (ETT) and connected to the ventilator via a disposable breathing circuit. Anesthesia was maintained with sevoflurane in an air-oxygen mixture (50%) at a flow rate of 2.0 L/min. An oxygen saturation of 98%–100% and normocapnia were maintained. Patient was placed supine with 10–15 degree head elevation. The head was turned slightly towards the right and fixed in a Mayfield Skull clamp. The surgical site was prepared, and the patient was draped using sterile sheets. The anesthesia machine was placed at the foot end on the left side of the patient with the breathing circuit running under the sterile surgical drapes connecting the ETT at the head end to the anesthesia machine at the foot end. A skin incision was made, and the skin flaps were retracted using a fishhook retractor.

Approximately 10 min after the start of surgery, collapse of the ventilator bellows with inability to deliver an adequate tidal volume and hypocapnia were noted. The ETT position, cuff pressure, circuit connection, and ventilator function were checked; however, no leaks were detected. The surgical procedure was stopped, the surgical clothes were carefully turned to one side to check the breathing circuit under the drape. On turning the drape, it was observed that the towel clip which was used to fix the fish hook retractor to the drapes, has pierced the breathing circuit underneath it and there were small holes in the circuit (Figs. 1A–C). The breathing circuit was replaced and no further leaks were detected. The rest of the intraoperative course was uneventful.

Leaks in the anesthesia circuit, which can lead to hypoxia, hy-

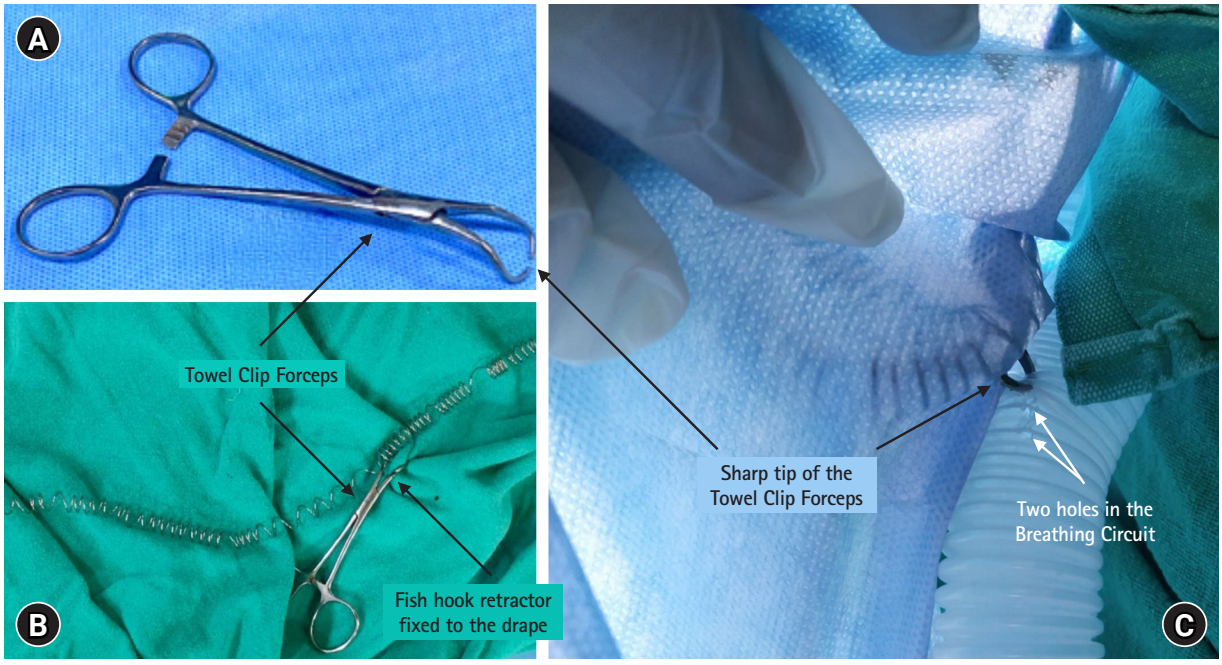

Fig. 1. The sharp tip of the towel clip forceps (A) was used to fix the fish hook retractor to the drape (B), which caused the holes in the breathing circuit (white arrows), which led to the leak in the breathing circuit (C).

poventilation, inadequate delivery of inhaled anesthetic gases, and contamination of the operating room, can be caused by disconnection or damage to the breathing circuit [3]. It can be detected by an audible leak sound, collapse of the breathing bag and ventilator bellows, inability to ventilate, decrease in oxygen saturation, fall in end tidal carbon dioxide, decrease in tidal volume and airway pressure [3,4]. Previous case reports have attributed corrugated circuit leaks to tube holders [3] and hot air fans [5]; however, the sharp tip of towel clip forceps is a unique finding. Thus, whenever anything is fastened to surgical drapes using a sharp object, feeling and identifying the objects underneath the surgical drapes, such as breathing circuits or intravenous tubing, is necessary to avoid unintentional damage. The routine practice of checking for leakage in the breathing system after draping can prevent major mishaps. Leaks in breathing circuits may lead to significant complications if they are not identified. Therefore, anesthesiologists' vigilance and preparedness in dealing with such situations can help prevent adverse outcomes.

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Peripherally inserted central catheters placed by anesthesiologists: an analysis of complications among 146 insertions

Peripherally inserted central catheters (PICCs) are inserted to provide central venous access for chemotherapy, frequent blood draws, nutrition, and antibiotic administration, among other indications. PICCs may be utilized on both an inpatient and outpatient basis, and are generally well tolerated and safe for extended use. Complication rates are generally related to the dwell time of the PICC and the severity of the patients' underlying medical conditions [1,2].

In anesthesiology, central venous access allows for central venous pressure (CVP) monitoring, aspiration of venous air embolisms, and effective hemodynamic control with vasoactive infusions in addition to providing additional access when peripheral circulation may be slowed (e.g., hypothermia) or unreliable (e.g., shock). The preferred sites for central line placement include the internal jugular, subclavian, or femoral veins; however, these sites are associated with variable rates of thrombosis, infections, pneumothorax, and other related complications [3]. The choice to place a central venous catheter at a particular site is made individually, considering the patients underlying health status [3–5].

Literature on the insertion of PICCs by anesthesiologists in the operating room as an alternative route for central venous access in adult patients is lacking. At our institution, many neuroanesthesiologists routinely place PICCs in adult patients in the operating room. Therefore, we conducted this single-center, retrospective study, which was approved by the Institutional Research Board of Stanford University (IRB no. 61180). Through a review of patient medical records, a total of 146 patients were identified as having undergone PICC insertion in the operating room by an anesthesiologist at our institution. Information on any complications associated with the PICCs were extracted from these medical records and categorized as either infections, thromboses, or organ or tissue injuries.

Five different anesthesiologists were the attending physicians for these 146 patients. The mean age of the patients was 47.4 years. A total of 75 males and 71 females were included in this study. Ninety-eight PICCs were placed on the right upper extremity and 48 on the left upper extremity. Sterile technique was observed at all times during insertion, and all patients had a chlorhexidine disc placed and received surgical site prophylactic antibiotics. In all cases, a 20-gauge intravenous catheter was placed under ultrasound guidance and a modified Seldinger technique was used to insert the PICC. Immediately following insertion, the CVP and CVP waveform were recorded and evaluated to ensure that the catheter tip position was consistent with central

venous placement. A postoperative chest radiography was performed in all patients.

All of the included patients underwent intracranial procedures, including 73 neurovascular cases, 72 brain tumor cases, and one epilepsy case. None of the patients underwent chest radiography before arriving in the recovery room or the intensive care unit. The placement of the PICCs was distributed among the four anatomical sites (antecubital veins: 103, axillary veins: 27, basilic veins: 15, and cephalic vein: 1). Six PICCs had to be withdrawn for repositioning based on postoperative chest radiography results. The average dwell time was 2.52 days, for a total of 368 catheter days. The dwell times of the PICCs are shown in Table 1.

No infections, thromboses, or organ or tissue injuries were reported in any of the 146 medical records reviewed. No cardiac arrhythmias were observed.

In adults, inserting a PICC as an alternative to conventional central line placement or to provide secondary access has several advantages. First, because they are inserted through a peripheral vein, the risk of pneumothorax is extremely low. Second, they can be placed when the patient is awake. This is especially advantageous for a patient who is expected to require vasoactive infusions shortly after the induction of anesthesia, as the placement of a central line may distract the anesthesiologist. Third, PICC removal should not place the patient at risk of venous air embolism because the venous pressure in the upper extremity should not be negative.

Among all the PICCs inserted in adult patients by anesthesiologists in the operating room included in this study, no infections, thromboses, or organ or tissue complications were reported. This is likely attributable to the short dwell time and routine use of prophylactic antibiotics. While a more extensive study is required to definitively establish the safety profile of PICC placement by anesthesiologists in the operating room, the absence of a single complication should aid in the promotion of widespread use of this technique for establishing central venous access.

Table 1. Dwell Time for Peripherally Inserted Central Catheters

Dwell time (days)	Number
1	36
2	72
3	20
4	4
5	4
6	2
7	4
8	0
9	0
10	2
11	0
12	0
13	0
14	0
15	0
16	0
17	0
18	1
19	0
20	1

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Corrosive poisoning and its implications on pediatric airways

Pharyngeal webs are a rare anomaly that occur after corrosive ingestion due to liquefaction necrosis (bases) or coagulation necrosis (acids). The mucosal lining heals by fibrosis, causing upper airway stenosis, synechiae, band formation, and esophageal stricture. In India, corrosive poisoning poses a large burden on the healthcare system, accounting for approximately 2% of the total cases of poisoning, and is associated with high morbidity and mortality, estimated at 50% and 13%, respectively [1].

For these patients, securing the airway is an anesthetic challenge owing to the distorted anatomy of the upper airway. Drooling and an inability to swallow indicate severe posterior pharyngeal or upper esophageal injury. The presence of hoarseness, stridor, nasal flaring, or rib retraction upon inhalation suggest airway involvement [2]. Multiple endoscopic or open procedures may be required to treat complications like pharyngeal and laryngeal webs, synichae and esophageal stricture. Airway management is thus both complicated and of paramount importance. Here, we discuss the challenges faced and measures taken to secure the airway in a pediatric patient with post-corrosive esophageal stricture posted for feeding jejunostomy.

A 14-year-old female with a history of corrosive poisoning in May 2022 presented with an esophageal stricture and was posted for feeding jejunostomy. She had previously undergone upper gastrointestinal endoscopy and esophageal dilatation six times. Preoperative airway examination revealed mouth opening of three fingers, a Mallampati score of II (Fig. 1A), stable vitals, and all routine investigations within normal limits. Written informed consent was obtained from the parents. Anticipating a difficult airway, the patient was attached to operation theatre standard monitors, with a fiberoptic flexible bronchoscope video scope (Storz®, Karl Storz Endoskope, Karl Storz Endoscopy India pvt Ltd., India) at the ready, and the cricothyroid membrane was marked using the laryngeal handshake technique. Pre-oxygenation was initiated with 100% oxygen using a closed circuit and intravenous (IV) fentanyl 2 μg/kg and propofol 2 mg/kg were administered for induction. A size 2.5 i-gel® supraglottic airway device (Intersurgical complete respiratory system, UK) was introduced, which had a significant leak. A size 3 i-gel® supraglottic airway device (Intersurgical complete respiratory system, UK) was then introduced, which also had a leak. As mask ventilation was possible, tracheal intubation using succinylcholine 1.5 mg/kg was conducted. Direct laryngoscopy revealed a distorted airway, with multiple visible webs and openings. The epiglottic tip was identified with great difficulty as it was embedded in the scar tissue. Because we were unsure of the location of the trachea, a fiberoptic bronchoscope was used for identification (Fig. 1B). The trachea was confirmed by direct visualization of the tracheal rings and carina, and the endotracheal tube was railroaded over the flexible bronchoscope (Fig. 1C). The position of the tube was confirmed by bronchoscopy and end-tidal CO_2. IV dexamethasone (8 mg), hydrocortisone (100 mg), and vecuronium (0.1 mg/kg) were administered after the effect of succinylcholine subsided. Anesthesia was maintained with 50% oxygen and 2 L total flow with sevoflurane at 1 minimum alveolar concentration. Once the surgical procedure was completed, the ENT team was called for endoscopy and ablation of the synechiae. The neuromuscular blocking agents were reversed with 100% oxygen, IV neostigmine (0.04 mg/kg body weight), and IV glycopyrrolate (0.01 mg/kg body weight). Once fully awake, the patient was extubated and transferred to the post-anesthesia care unit for observation.

Although the airway examination was normal in the preoperative evaluation, a difficult airway should be anticipated in patients with a history of corrosive poisoning and appropriate arrangements should be made. The use of a laryngeal mask airway is limited to patients with normal upper airway anatomy and is thus seldom used in those with distorted airway conditions. The hallmark of management in these cases includes preservation of spontaneous ventilation until confidence in the airway is reached following laryngoscopy. Intubation must be performed under visual guidance to avoid passage into a false track or incorrect placement of endotracheal tube [3].

Airway mismanagement remains an important cause of mortality and morbidity in anesthetic practice. Conventional rigid direct laryngoscopy aids tracheal intubation in 98.1% of the cases [4]. Thus, alternative equipment and techniques must be readily available for the re-

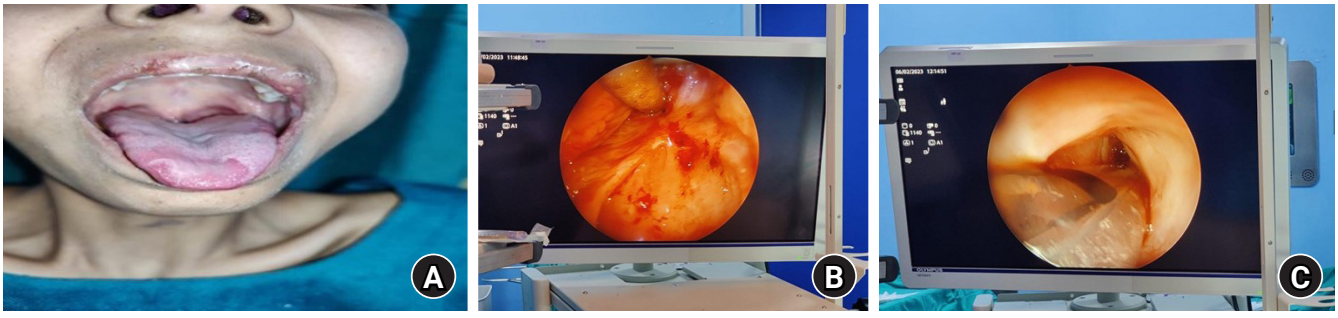

Fig. 1. (A) Modified Mallampati score of II. (B) Pharyngeal web seen on fiberoptic bronchoscopy. (C) Endotracheal tube passing through the vocal cords.

maining 1.9% of cases. These patients can also have tracheal stenosis; thus, a preoperative neck radiograph (AP, lateral view) or computed tomography is advised, and smaller endotracheal tubes and a backup for front-of-neck access should be arranged.

We conclude that every case of post-corrosive poisoning, acute or chronic, that requires tracheal intubation should be defined as a difficult airway case and appropriate arrangements according to available guidelines must be made to prevent airway mishaps [5].

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The novel diagonal suprascapular canal block for shoulder surgery analgesia: a comprehensive technical report

A combination of the sub-omohyoid suprascapular nerve (SSN) block and subscapularis plane (SSP) block can be administered to provide a "shoulder block." This innovative block is performed through an anterior approach and blocks the lower and upper subscapular nerves and axillary nerve at a proximal level [1].

Despite the evident benefits of this technique for shoulder surgery, the articular branch of the lateral pectoral nerve, supraclavicular branches of the cervical plexus, and musculocutaneous nerve are not affected The main advantage of this combined shoulder block compared with other techniques, such as the interscalene block, is the reduction in the motor and sensory block of the upper limbs and minimal phrenic paralysis [1,2].

Due to the more selective and safer profile of this shoulder block compared with other techniques, highly concentrated (low-volume) local anesthetics may be given in single-shot administrations to prolong the duration of the blockade, contributing to a painless first postoperative night [3]. The anterior approach of these blocks is paramount to minimizing patient discomfort and simplifying the procedure, which is particularly relevant in the trauma setting. However, most studies on the sub-omohyoid SSN block have shown a lack of brachial plexus or phrenic nerve sparing in several patients [4].

The prevertebral fascia only separates the SSN from the brachial plexus at the lateral sub-omohyoid plane. Therefore, even though the needle does not penetrate the fascia, in most cases the local anesthetic may spread to parts of the plexus. In fact, a study by Siegenthaler et al. [4] demonstrated that the median distance from the SSN to the brachial plexus was only 9 mm (range 4–18 mm) among 60 healthy volunteers. In a cadaveric study using 5 ml of dye, mild staining of the phrenic nerve was found in two of the nine dissections [5].

Due to the risk of phrenic nerve involvement, the sub-omohyoid SSN block may not be recommended for high-risk pulmonary patients. Additionally, this block is associated with a risk of significant upper limb sensory and motor block. Indeed, the target site for the sub-omohyoid SSN block is the region where the SSN exits out of the prevertebral compartment after coursing beneath the inferior belly of the omohyoid muscle (OHM) and branching off from the superior trunk.

The novel diagonal suprascapular canal (DiSC) block has been proposed to diminish these risks associated to sub-omohyoid SSN block. For the DiSC block, an anterior approach is used (in the supine position) away from the prevertebral compartment. In contrast to the sub-omohyoid SSN block, the DiSC block is performed along the suprascapular canal (SSC) from a superior incision point that accompanies the track of the SSN diagonally between the suprascapular and the spinoglenoid notches. In our approach for the "shoulder block", the DiSC block is combined with an SSP block.

After traveling posteriorly to the OHM, the SSN passes over the serratus anterior muscle (second rib level) and enters the supraspinatus fossa through the suprascapular notch.

In a cadaveric study, the SSN was found to bifurcate into the medial (MT) and lateral (LT) trunks at the suprascapular notch level, coursing along the floor of the supraspinous fossa to supply muscular and articular sensory innervation [5].

The MT has been found to primarily provide motor innervation to the anterior region of the supraspinatus, whereas the LT provides articular branches to the glenohumeral joint and motor innervation to the posterior region of the supraspinatus as well as the superior, middle, and inferior regions of the infraspinatus [5]. Articular branches of the SSN, which supply the posterior glenohumeral joint, have been reported to consistently originate from the LT close to the midpoint of a line connecting the suprascapular and spinoglenoid notches [5].

For this procedure, the patient is maintained in the supine position and a curvilinear probe is placed coronally at the level of the supraclavicular fossa, immediately posterior to the lateral third of the clavicle

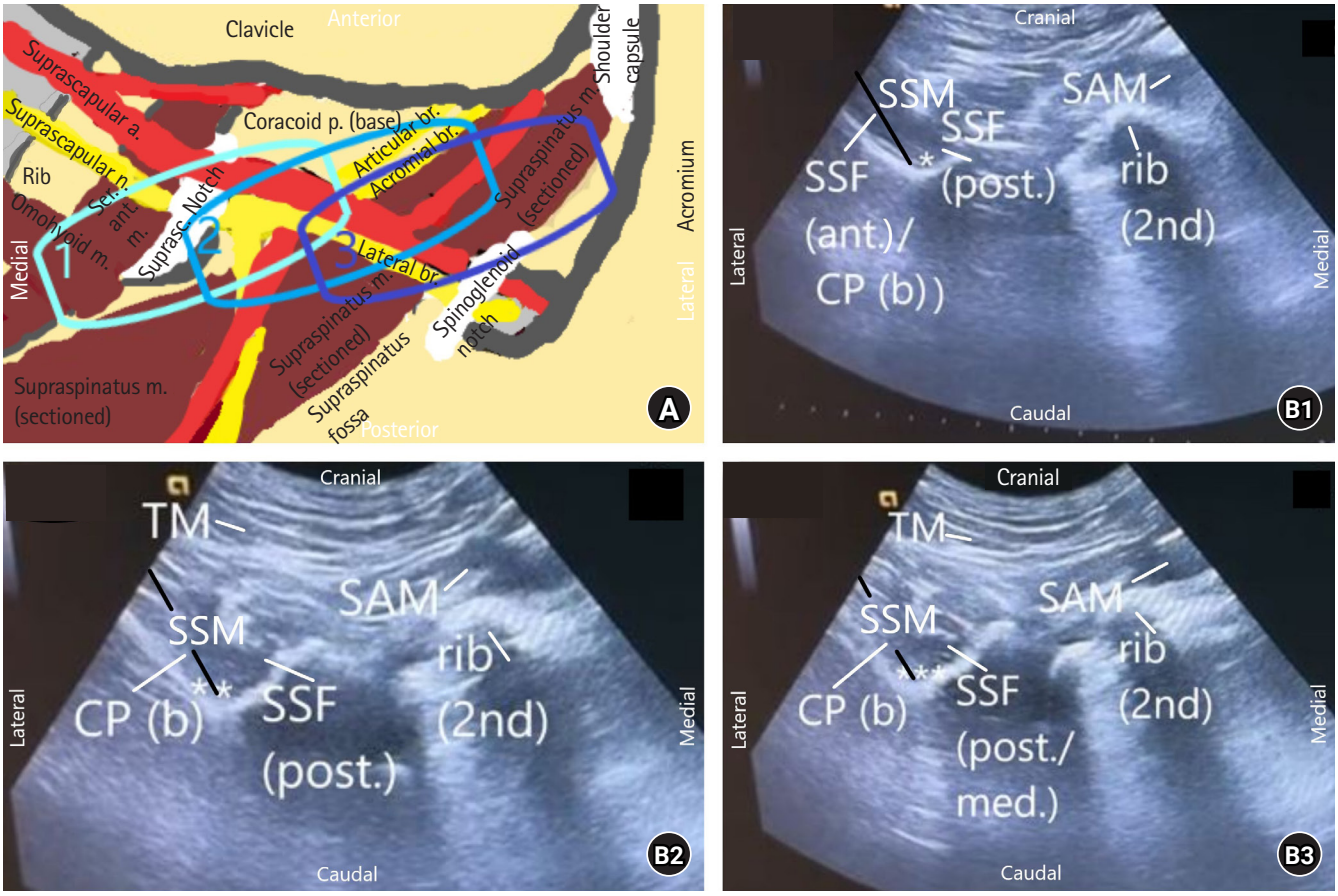

Fig. 1. Description of the novel diagonal suprascapular canal block. (A) Schematic representation of the relevant anatomy for performing the novel diagonal suprascapular canal block (vertical view with the supraspinatus muscle sectioned in its course is shown for visualization of the underlying structures). Relevant movements and adjustments of the probe are shown. As the position of the probe varies slightly (geometric forms 1, 2, and 3 are colored different shades of blue), different ultrasound images are shown for B1–B3 (labeled using the corresponding shades of blue). (B1–B3) Relevant sonoanatomy for performing the novel diagonal suprascapular canal block. Images were obtained at different points on the supraspinatus fossa. The vessels are barely visible in this diagonal view using a low-frequency probe despite the eventual use of the colored Doppler ultrasound image; therefore, the suprascapular vessels are not identified. (B1) At the entrance of the SSC (suprascapular notch), the slopes of the ultrasound SSC valley are less steep but at the bottom of that valley, the ultrasound beam penetrates deeply due to the lack of bony structures. At this point, by tilting the probe posteriorly or laterally, a complete ultrasound SSC valley can be visualized (B1 corresponds to ultrasound position 1 in A). (B2) By moving the probe posteriorly or laterally, the ultrasound SSC valley can be seen to continue fully formed (B2 corresponds to position 2 in A). (B3) In this position, the complete bony shadow starts vanishing (i.e., the bottom of the ultrasound SSC valley disappears), corresponds to the spinoglenoid notch (B3 corresponds to position 3 in A). At this point, by tilting the probe posteriorly or laterally, the SGNo is identified where the ultrasound beam starts to enlarge, traversing to deeper structures, which confirms that the prior image at position 3 is accurate. At the level of the suprascapular notch, the borders of the "valley" are less steep. The black lines in the ultrasound images represent the insertion of the needle in-plane at different positions. Ser. Ant. m. or SAM: serratus anterior muscle, SSF: scapular supraspinous fossa, post: posterior, ant: anterior, med: medial, lat: lateral, MB: medial branch, LB: lateral branch, m: muscle, a: artery, CP (b): coracoid process base. *suprascapular canal at the level of the suprascapular notch, **midpoint of the suprascapular canal, ***suprascapular canal at the level of the spinoglenoid notch.

(caudally oriented). The acromion remains immediately lateral to the probe. Ultrasound imaging allows for the borders of the SSC to be visualized, forming a triangle-shaped "valley." The borders of this valley are formed medially by the supraspinatus fossa and laterally by the base of the coracoid process. When the probe is slid in the posterior, medial-to-anterior, or lateral direction, the ultrasound beam reaches the spinoglenoid notch (lateral to this point, the floor of the SSC vanishes from view) (Fig. 1).

A total of 5–8 ml of local anesthetic is injected deep into the supraspinatus muscle (located beneath the trapezius muscle). The suprascapular artery may be observed at the bottom of the triangle-shaped valley but not at the suprascapular notch because it travels superiorly to the suprascapular ligament. The needle is inserted in-plane but can also be inserted out-of-plane medial to the acromion.

The use of a curvilinear probe is essential for performing a DiSC block because it allows a broad panoramic sonoanatomical view. With the DiSC block technique, all the SSN rami involved in shoulder innervation can be effectively blocked using a diagonal view of the SSC. On the other hand, an injection near the spinoglenoid notch may provide less of a supraspinatus motor block, sparing the lateral trunk, but may fail to provide significant shoulder analgesia [5]. Conversely, an injection in the vicinity of or beyond the spinoglenoid notch is easily noted with the DiSC block (Fig. 1).

Patients with rotator cuff tears involving the supraspinatus, infraspinatus, glenohumeral joint, or capsule pathology consistently feel pain relief after a DiSC block in the preoperative setting, which results in an increase in preoperative range of motion due to higher comfort with movements involving the deltoid and trapezius muscles. No motor block or loss of thermal sensation is observed distal to the shoulder. Further studies are required to confirm the feasibility of this approach.

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Under any circumstances, the identities of the reviewers will not be revealed and the reviewers will be blinded to the names of the authors and the institutions from which the manuscripts have been sent. Submitted manuscripts will be reviewed by 2 or more experts in the corresponding field. The Editorial Board may request authors to revise the manuscripts according to the reviewer's opinion. After revising the manuscript, the author should upload the revised files with a reply to each item of the reviewer's opinion. The author's revisions should be completed within 30 days after the request. If it is not received by the due date, the Editorial Board will not consider it for publication again. To extend the revision period to more than 30 days, the author should negotiate with the Editorial Board. The manuscript review process should be finished the second review. If the authors wish further review, the Editorial Board may consider it. The Editorial Board will make a final decision on the approval for publication of the submitted manuscripts and can request any further corrections, revisions, and deletions of the article text if necessary. Statistical editing is also performed if the data need professional statistical review by a statistician. The review and publication processes that are not described in the Instructions for Authors will be incorporated into the Editorial Policy Statements approved by the Council of Science Ed-

itors Board of Directors, available at: www.councilscienceeditors.org/.

5. Article processing charge and publication fee

There is no charge for submitting and processing a paper until policy change. But, the KJA charges a publication fee for each printed page of KRW. Publication fees are waived if the affiliation of corresponding author is outside Korea.

6. Copyrights

Copyrights of all published materials are owned by the KSA. On behalf of co-author(s), corresponding author must complete and submit the journal's copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (http://www.icmje.org/recommendations/). A copy of the form (https://ekja.org/authors/copyright_transfer_agreement.php) is made available to the submitting author within the Editorial Manager submission process.

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KJA is an open access journal. Accepted peer-reviewed articles are freely available on the journal website for any user, worldwide, immediately upon publication without additional charge. Articles are distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. To use the tables or figures of KJA in other periodicals, books or media for scholarly, educational purposes, the process of permission request to the publisher of KJA is not necessary. This is in accordance with the Budapest Open Access Initiative definition of open access. It also follows the open access policy of PubMed Central at United States National Library of Medicine (http://www.ncbi.nlm.nih.gov/pmc/). All the content of the journal is available immediately upon publication without embargo period.

Research and publication ethics

For the policies on research and publication ethics that are not stated in these instructions, the Good Publication Practice Guidelines for Medical Journals, available at: https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=13, or the Guidelines on Good Publication, available at: publicationethics.org/, can be applied.

1. Conflict-of-interest statement

Conflict of interest exists when an author or the author's institution, reviewer, or editor has financial or personal relationships that inappropriately influence or bias his or her actions. Such relationships are also known as dual commitments, competing interests, or competing loyalties. These relationships vary from being negligible to having a great potential for influencing judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects his or her scientific judgment. Financial relationships such as employment, consultancies, stock ownership, honoraria, and paid expert testimony are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, or of the science itself. Conflicts can occur for other reasons as well, such as personal relationships, academic competition, and intellectual passion (http://www.icmje.org/conflicts-of-interest/). If there are any conflicts of interest, authors should disclose them in the manuscript. The conflicts of interest may occur during the research process as well; however, it is important to provide disclosure. If there is a disclosure, editors, reviewers, and reader can approach the manuscript after understanding the situation and the background of the completed research.

2. Statement of informed consent and Institutional Review Board approval

If the study in the article is on human subjects or human-originated material, informed consent for the study and the Institutional Review Board (IRB) approval number needs to be provided. Copies of written informed consents and IRB approval for clinical research should be kept. If necessary, the editor or reviewers may request copies of these documents to make potential ethical issues clear.

3. Statement of human and animal right

Clinical research should be done in accordance of the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Helsinki Declaration of 1975 (revised 2013) (available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Authors should indicate whether the procedures were conducted in accordance with the Helsinki Declaration-2013 in the Text. Clinical studies that do not meet

the Helsinki Declaration will not be considered for publication. Human subjects should not be identifiable, such that patients' names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. For animal subjects, research should be performed based on the National or Institutional Guide for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

4. Registration of the clinical trial research

Any researches that deals with clinical trial should be registered with the primary national clinical trial registration site such as Korea Clinical Research Information Service (cris.nih.go.kr/) or other sites accredited by WHO or International Committee of Medical Journal Editor such as ClinicalTrials.gov (clinicaltrials.gov/).

5. Reporting guidelines

The KJA recommends a submitted manuscript to follow reporting guidelines appropriate for various study types. Good sources for reporting guidelines are the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network (www.equator-network.org/) and the U.S. National Library of Medicine's (NLM's) Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html). The appropriate checklist (and flow diagram, if applicable) must be included with each submission.

6. Authorship

Authorship credit should be based on: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; AND 2) drafting the article or revising it critically for important intellectual content; AND 3) final approval of the version to be published; AND 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these 4 conditions. If the number of authors is equal to or greater than 2, there should be a list of each author's role in the submitted paper. Authors are obliged to participate in peer review process. All others who contributed to the work who are not authors should be named in the Acknowledgements section. KJA has a strict policy on changes to authorship after acceptance of the article and will only consider changes in the most extraordinary situations once the article is accepted.

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Plagiarism is the use of previously published material without attribution. The KJA editorial office screens all submitted manuscripts for plagiarism, using a sophisticated software program, prior to peer review. When plagiarism is detected at any time before publication, the KJA editorial office will take appropriate action as directed by the standards set forth by the Committee on Publication Ethics (COPE). For additional information, please visit http://www.publicationethics.org. It is mandatory for all authors to resolve any copyright issues when citing a figure or table from a different journal that is not open access.

8. Secondary publication

It is possible to republish manuscripts if the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, available at: www.icmje.org/.

9. Feedback after publication

If the authors or readers find any errors, or contents that should be revised, it can be requested from the Editorial Board. The Editorial Board may consider erratum, corrigendum or a retraction. If there are any revisions to the article, there will be a CrossMark description to announce the final draft. If there is a reader's opinion on the published article with the form of Letter to the editor, it will be forwarded to the authors. The authors can reply to the reader's letter. Letter to the editor and the author's reply may be also published.

9-1. Process to manage the research and publication misconduct

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of KJA will discuss the suspected cases and reach a decision. KJA will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

9-2. Policy of Article withdrawal, retraction, and replacement

1) Article withdrawal

Articles in Press (articles that have been accepted for publication but which have not been formally published and will not yet have the complete volume/issue/page information) that include errors, or are discovered to be accidental duplicates of

other published article(s), or are determined to violate our journal publishing ethics guidelines in the view of the editors (such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like), may be "Withdrawn".

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Errors serious enough to invalidate a paper's results and conclusions (Infringements of professional ethical codes, such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like) may require retraction.

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Replacement (retraction with republication) can be considered in cases where honest error (e.g., a misclassification or miscalculation) leads to a major change in the direction or significance of the results, interpretations, and conclusions. If the error is judged to be unintentional, the underlying science appears valid, and the changed version of the paper survives further review and editorial scrutiny, then replacement of the changed paper, with an explanation, allows full correction of the scientific literature.

See also the National Library of Medicine's policy on retractions and the recommendations of the International Committee of Medical Journal Editors (ICMJE) concerning corrections and retractions, or https://publicationethics.org/resources/guidelines.

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KJA adheres to COPE guidelines regarding appeals to editorial decisions and complaints. For additional information, please visit https://publicationethics.org/core-practices.

Data sharing statement

KJA accepts the ICMJE Recommendations for data sharing statement policy (http://icmje.org/icmje-recommendations.pdf). All manuscripts reporting clinical trial results should submit a data sharing statement following the ICMJE guidelines from 1 July 2018. Authors may refer to the editorial, "Data Sharing statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors," in Annals on 6 June 2017 (http://www.icmje.org/news-and-editorials/data_sharing_june_2017.pdf).

Submitting manuscripts in preprint archives

A preprint is a preliminary version of a scientific article that is posted online at publicly accessible repositories before undergoing a formal peer review in a traditional academic journal.

Authors are encouraged to submit the final versions of their preprints to KJA without treating them as duplicate submissions or publications. During the manuscript submission process, authors should disclose the preprint's DOI to exclude it from the estimation of the similarity index for the final manuscript. We will conceal the preprint's DOI to blind peer reviewers to the authors' list. Any differences between the authors' list of the final manuscript submitted to KJA and the preprint should be minimal and will require a thorough explanation. After acceptance for publication, authors will be asked to update the meta-information of the preprint to point to the DOI of the final published article in KJA.

Articles published without peer review, including preprints, abstracts of conferences, and American Society of Anesthesiologists (ASA) refresher course lectures, may not be included in the references.

Manuscript preparation

1. Word processors and format of manuscript

A manuscript must be written in proper and clear English. The manuscript, including tables and their footnotes, and figure legends, must be typed in one double space. Materials should be prepared with a standard 12-point typeface or greater (Times New Roman typeface is preferred). The manuscript should be in the following sequence: cover letter (optional), title page file, manuscript (title and running title, abstract and keywords, introduction, materials and methods, results, discussion, references, tables, and figure legends), figures, other submission elements. All pages should be numbered consecutively starting from the title page. All numbers should be written in Arabic numerals throughout the manuscripts. Our preferred file format is DOCX or DOC. A single PDF file that contains all materials in a file including figures and figure legends is acceptable. In that case, authors should add line numbers throughout the document. Manuscript containing anything in headers and footers, except of page numbers, will be returned to authors. If your PDF submission is accepted, you will be asked to upload your final document file in DOCX or DOC format as well. Make sure to update your PDF file with the most recent version of your manuscript.

2. Abbreviation of terminology

Abbreviations should be avoided as much as possible. When they are used, full expression of the abbreviations following the abbreviated word in parentheses should be given at the first use. Common abbreviations, however, may be used, such as DNA. Abbreviation can be used if it is listed as a MeSH subject heading (http://www.ncbi.nlm.nih.gov/mesh).

3. Word-spacing

1) Leave 1 space for each side, using arithmetic marks as +, −, ×, etc.

Leave no space for hyphen between words.

2) Leave 1 space after " , " and " ; ". Leave 2 spaces after " . " and " : ".

3) Using parentheses, leave 1 space each side.

4) Brackets in parentheses, apply square brackets.

4. Citations

1) If a citation has 2 authors, write as "Hirota and Lambert." If there are more than 3 authors, apply 'et al.' at the end of the first author's surname. Ex) Kim et al. [1].

2) Citation should be applied after the last word or author's surname.

3) Apply citation before a comma or period.

4) Identify reference by several or coupled Arabic numbers, enclosed in square brackets on the line as [1,3,5].

5. Arrangement of manuscript

All articles should be arranged in the following order.

Cover letter (optional)

Title Page file, uploaded separately

Manuscript, as a single file in word processing format (eg, . doc), consisting of Title and running title, Abstract (if required for the article type; see relevant section), Body Text, References, Tables, Figure Legends, if any (in numerical order, on the same page); be sure to number all pages of the manuscript file

Figures (each Figure should be a separate file in figure file format)

Other submission elements (Supplemental Digital Content, etc.)

Each new section's title should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page. Page numbers should be placed at the middle of the bottom of page. For survey-based clinical studies, the original survey document does not need to be included in the body of the manuscript but may be supplemented in an appendix.

6. Statistical Analysis

1) Describe the statistical tests employed in the study with enough detail so that readers can reproduce the same results if the original data are available. The name and version of the statistical package should be provided.

2) Authors should describe the objective of the study and hypothesis appropriately. The primary/secondary endpoints are predetermined sensibly according to the objective of the study.[1]

3) The characteristics of measured variables should determine the use of a parametric or nonparametric statistical method. When a parametric method is used, the authors should describe whether the basic statistical assumptions are met.[2,3]

4) For an analysis of a continuous variable, the normality of data should be examined. Describe the name and result of the particular method to test normality.

5) When analyzing a categorical variable, if the number of events and sample is small, exact test or asymptotic method with appropriate adjustments should be used. The standard chi-squared test or difference-in-proportions test may be performed only when the sample size and number of events are sufficiently large.

6) The Korean Journal of Anesthesiology (KJA) strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. In addition, the uncertainty of estimated values, such as the confidence interval, should be described consistently in figures and tables.[4]

7) Except for study designs that require a one-tailed test, for example, non-inferiority trials, the P values should be two-tailed. A P value should be expressed up to three decimal places (not as "$P < 0.05$"). If the value is less than 0.001, it should be described as "$P < 0.001$" but never as "$P = 0.000$." For large P value greater than 0.1, the values can be rounded off to one decimal place, for example, $P = 0.1$, $P = 0.9$.

8) A priori sample size calculation should be described in detail.[5] Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent.

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[1]Lee S, Kang H. Statistical and methodological considerations for reporting RCTs in medical literature. Korean J Anesthesiol 2015; 68: 106-15.

[2]Kim TK. T test as a parametric statistic. Korean J Anesthesiol 2015; 68: 540-6.

[3]Nahm FS. Nonparametric statistical tests for the continuous data: the basic concept and the practical use. Korean J Anesthesiol 2016; 69: 8-14.

[4]Park S. Significant results: statistical or clinical? Korean J Anesthesiol 2016; 69: 121-5.

[5]In J. Considerations when calculating the sample size for an inequality test. Korean J Anesthesiol 2016; 69: 327-31.

In the case of multiple comparisons, an adjusted level of significance is acceptable.[6]

9) It is recommended using mean ± SD or median (Q1, Q3) format to present representative values of continuous variables. Results must be written in significant figures. The measured and derived numbers should be rounded off to reflect the original degree of precision. Calculated or estimated numbers (such as mean and SD) should be expressed in no more than one significant digit beyond the measured accuracy. Therefore, the mean ± SD of body weight in patients measured on a scale that is accurate to 0.1 kg should be expressed as 65.45 ± 2.52 kg.

10) Except when otherwise stated herein, authors should conform to the most recent edition of the American Medical Association Manual of Style.[7]

7. Organization of manuscript

1) Clinical or Experimental research

(1) Title page

① Title

Title should be concise and precise.

For the title, only the first letter of the first word should be capitalized.

② Author information

First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly.

③ Running title

A running title of no more than 40 characters, including letters and spaces, should be described. If inappropriate, the editorial board may revise it.

④ Corresponding Author

Name, mailing address, phone number, and e-mail address of the corresponding author

⑤ Previous presentation in conferences

Title of the conference, date of presentation, and the location of the conference may be described.

⑥ Conflict of interest

It should be disclosed here according to the statement in the Research and publication ethics regardless of existence of conflict of interest. If the authors have nothing to disclose, please state: "No potential conflict of interest relevant to this article was reported."

⑦ Funding

Funding to the research should be provided here. Providing a FundRef ID is recommended including the name of the funding agency, country and if available, the number of the grant provided by the funding agency. If the funding agency does not have a FundRef ID, please ask that agency to contact the FundRef registry (e-mail: fundref.registry@crossref.org). Additional detailed policy of FundRef description is available from http://www.crossref.org/fundref/.

⑧ Acknowledgments

Any persons that contributed to the study or the manuscript, but not meeting the requirements of an authorship could be placed here. For mentioning any persons or any organizations in this section, there should be a written permission from them.

⑨ IRB number

⑩ Clinical trial registration number

If any of these elements are not applicable to your submission, write "not applicable" after the number and topic; for example, "Prior Presentations: Not applicable."

(2) Manuscript

① Title and Running title

② Abstract

All manuscripts should contain a structured abstract that is written only in English. Provide an abstract of no more than 250 words. It should contain 4 subsections: Background, Methods, Results, and Conclusions. Quotation of references is not available in the abstract. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicomma (;), and mark a period (.) at the end of the last word.

③ Introduction

The introduction should address the purpose of the article concisely and include background reports that are relevant to the purpose of the paper.

④ Materials and Methods

· The materials and methods section should include sufficient details of the design, subjects, and methods of the article in order, as well as the data analysis methods and con-

[6]Lee S and Lee DK. What is the proper way to apply the multiple comparison test? Korean J Anesthesiol 2018; 71: 353-60.

[7]http://www.amamanualofstyle.com/

trol of bias in the study. Sufficient details need to be addressed in the methodology section of an experimental study so that it can be further replicated by others.

· When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the IRB for the study and the IRB approval number needs to be provided. When reporting experiments with animal subjects, the authors should indicate whether the handling of the animals was supervised by Institutional Board for the Care and Use of Laboratory Animals. "American Society of Anesthesiologists physical status classification" should not be abbreviated. As a rule, subsection titles are not recommended.

· Clearly describe the selection of observational or experimental participants. Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). For additional information, please visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/.

· Reports of randomized trials must conform to the revised CONSORT guidelines and should be submitted with the CONSORT flow diagram. The CONSORT checklist should be submitted as a separate file along with the manuscript. The CONSORT statement, checklist, and flow diagram can be found at http://www.consort-statement.org or EQUATOR Network (https://www.equator-network.org/home/)

· Units

Laboratory information should be reported in International System of Units [SI]. Please refer to A Guide for Biological and Medical Editors and Authors, 6th Edn. Baron DN and Clarke HM, ed. (2008), CRC Press. or visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/

· Exceptions

A. The unit for volume is "l", others in "dl, ml, μl".

B. The units for pressure are mmHg or cmH_2O.

C. Use Celsius for temperature

D. Units for concentration are M, mM, μM.

E. When more than 2 items are presented, diagonal slashes are acceptable for simple units. Negative exponents should not be used.

F. Leave 1 space between number and units.

Exception) 5%, 36°C

· Machines and Equipment

According to the 11th edition of the American Medical Association, provide the model name and manufacturer's name without the country.

· Drug Names

Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide ® or ™ as a superscript and the manufacturer's name.

· Ions

Ex) Na^+ [O], Mg^{2+} [O], Mg^{++} [X], Mg^{+2} [X]

· Statistics

Statistical methods must be described with enough detail so that readers can reproduce the same results if the original data available. The KJA strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. A sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint.

⑤ Results

Results should be presented in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all of the data in the tables or illustrations in the text; emphasize or summarize only the most important observations. Results can be sectioned by subsection titles but should not be numbered. Citation of tables and figures should be provided as Table 1 and Fig. 1.

⑥ Discussion

The discussion should be described to emphasize the new and important aspects of the study, including the conclusions. Do not repeat the results in detail or other information that is given in the Introduction or the Results section. Describe the conclusions according to the purpose of the study but avoid unqualified statements that are not adequately supported by the data. Conclusions may be stated briefly in the last paragraph of the Discussion section.

⑦ References

The description of the journal reference follows the descriptions below. Otherwise, it follows the NLM Style Guide for Authors, Editors, and Publishers (Patrias, K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling, DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007 [updated 2009 Jan 14; cited 2009 May 1]. Available at: www.nlm.nih.gov/citingmedicine).

· References should be obviously related to documents and should not be exceed 50. For exceeding the number of references, it should be negotiated with the Editorial Board. References should be numbered consecutively in the order in which they are first mentioned in the text. Provide footnotes in the body text section. All of the references should be stated in English, including author, title, name of journal, etc.
· If necessary, the editorial board may request original documents of the references.
· The journal title should be listed according to the List of Journals Indexed for MEDLINE, available at: www.nlm.nih.gov/archive/20130415/tsd/serials/lji.html or the List of KoreaMed Journals, available at: koreamed.org.
· Six authors can be listed. If more than 6 authors are listed, only list 6 names with 'et al.'
· Provide the start and final page numbers of the cited reference.
· Abstracts of conferences are not allowed to be included in the references. The American Society of Anesthesiologists (ASA) refresher course lecture is not acceptable as a reference.
· Description format

A. Regular journal

Author name. Title of journal Name of journal published year; volume: start page-final page.

Ex) Rosenfeld BA, Faraday N, Campbell D, Dorman T, Clarkson K, Siedler A, et al. Perioperative platelet activity of the effects of clonidine. Anesthesiology 1992; 79: 256-61.

Ex) Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. Br J Anaesth 1996; 77: 441-4.

Ex) Kang JG, Lee SM, Lim SW, Chung IS, Hahm TS, Kim JK, et al. Correlation of AEP, BIS, and OAA/S scores under stepwise sedation using propofol TCI in orthopedic patients undergoing total knee replacement arthroplasty under spinal anesthesia. Korean J Anesthesiol 2004; 46: 284-92.

Ex) '2006; 7(Suppl 1): 64-96' '2007; 76: H232-8'

B. Monographs

· Author. Book name. Edition. Place, press. Published year, pp (start page)-(End page).
· If reference page is only 1 page, mark 'p'.
· Mark if it is beyond the 2nd edition.

Ex) Nuwer MR. Evoked Potential monitoring in the operating room. 2nd ed. New York, Raven Press. 1986, pp 136-71.

C. Chapter

Ex) Blitt C. Monitoring the anesthesized patient. In: Clinical Anesthesia. 3rd ed. Edited by Barash PG, Cullen BF, Stoelting RK: Philadelphia, Lippincott-Raven Publishers. 1997, pp 563-85.

D. Electronic documents

Ex) Grainge MJ, Seth R, Guo L, Neal KR, Coupland C, Vryenhoef P, et al. Cervical human papillomavirus screening among older women. Emerg Infect Dis [serial on the Internet]. 2005 Nov [2005 Nov 25]. Available from wwwnc.cdc.gov/eid/article/11/11/05-0575_article

E. Online journal article

Ex) Sampson AL, Singer RF, Walters GD. Uric acid lowering therapies for preventing or delaying the progression of chronic kidney disease. Cochrane Database Syst Rev 2017; 10: CD009460.

F. Papers that have been submitted and accepted for publication should be included in the list, with the phrase 'in press' replacing volume and page number. Authors should be prepared to give the volume and page number at the time of proof correction.

Ex) Baumbach P, Gotz T, Gunther A, Weiss T, Meissner W. Chronic intensive care-related pain: Exploratory analysis on predictors and influence on health-related quality of life. Eur J Pain 2017. Advance Access published on Nov 5, 2017. doi:10.1002/ejp. 1129.

⑧ Table

· Type or print each table on a separate sheet of paper.
· Number tables consecutively in the order of their first citation in the text.
· Supply a brief title

Tables should be more than 4 rows and should not be over 1 page.

· Except for titles and first letters, all of the text in the tables should be written in small alphabetic letters.
· In demographic data, sex would be provided as M/F, and age in yr. Data of year, weight, height, and any other units would be provided with 1 decimal place.
· "±" sign in the upper column of table should be lined up with the lower column.
· Footnotes should be provided consecutively in order of the cited tables or statistics.
· Marks for footnote should be given in order of *, †, ‡, §, ‖, ¶, **, ††, ‡‡... When marks are used to explain items of the table, indicate them with superscripts.
· Define all abbreviations except those approved by the International System of Units. Define all abbreviations every

time they are repeated.

⑨ Legends for figures and photographs

· All of the figures and photographs should be described in the text separately.

· The description order is the same as in the footnotes in tables and should be in recognizable sentences.

· Define all abbreviations every time they are repeated.

(3) Figures and illustrations

① The KJA publishes in full color, and encourages authors to use color to increase the clarity of figures. Please note that color figures are used without charge for online reading. However, since it will be charged upon the publication, authors may choose to use colors only for online reading.

② Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray). Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink). Figure backgrounds and plot areas should be white, not gray. Axis lines and ticks should be black and thick enough to clearly frame the image. Axis labels should be large enough to be easily readable, and printed in black.

③ Figures should be uploaded as separate tif, jpg, pdf, gif, ppt files. Width of figure should be 84 mm (one column). Contrast of photos or graphs should be at least 600 dpi. Contrast of line drawings should be at least 1,200 dpi. Number figures as "Fig. (Arabic numeral)" in the order of their citation. (ex. Fig. 1).

④ Photographs should be submitted individually. If Figure 1 is divided into A, B, C and D, do not combine it into 1, but submit each of them separately. Authors should submit line drawings in black and white.

⑤ In horizontal and vertical legends, the letter of the first English word should be capitalized.

⑥ Connections between numbers should be denoted by "-", not "~". Do not space the numbers (ex. 2–4).

⑦ Figures (line drawings) should be clearly printed in black and white.

⑧ Figures should be explained briefly in the footnotes. The format is the same as the table format.

⑨ An individual should not be recognizable in the photographs or X-ray films unless written consent of the subject has been obtained and is provided at the time of submission.

⑩ Pathological samples should be pictured with a measuring stick.

(4) Other submission elements (Video submission)

The KJA publishes supplemental video (movie) clip(s) that will be available online. Not only recording of the abstract, text, audio or video files, but also data files should be added here.

Each video clip should clearly illustrate the primary findings within an adequate amount of viewing time and be discussed in the text. Authors should provide appropriate labeling (e.g., arrows, abbreviations of anatomic structures, etc.) in the video clips. However, all identifying information, including patient name and/or ID number, hospital name, and date of the procedure, should be removed.

Video clips should contain succinct teaching points that must be supported by the current literature or standard reference texts, preferably those most accessible to the general reader. The adequacy of the teaching points will be evaluated during the review process and finally confirmed by the editorial board at the end of the review process.

Video clips are uploaded as the last file(s) at the time of manuscript submission and should be marked as supplementary video files.

① The video clip(s) should have simple file names (e.g., Video 1***, Video 2***) and include the appropriate extension (e.g., .mov, .mpg).

② The maximum number of video clips is 20.

③ The video clip(s) should be playable on both Windows and MAC computers. The video clip(s) should be tested for playback before submission, preferably on computers not used for their creation, to check for any compatibility issues.

④ Individual video files should be a minimum of 480 x 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been made with the editorial board prior to submission. Approval of files of > 2 GB will be made at the end of the review process.

⑤ Supplemental still images that correspond to the respective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).

2) Systematic review and meta-analysis

Systematic reviews are systematic, critical assessments of literature and data sources in order to answer a specific question, and/or includes a statistical technique leading to a quantitative summary of results and examining sources of differences in results among studies, if any. The subtitle should include the phrase "A systematic review" and/or "A Meta-analysis."

Organization of systematic review and meta-analysis: Same as clinical and experimental studies, except,

· All systematic reviews and meta-analyses should be regis-

tered at an appropriate online public registry (eg, PROSPERO; http://www.crd.york.ac.uk/PROSPERO/), and registration information should be included with the submission.

· Authors of reports of meta-analyses of clinical trials should submit the PRISMA flow diagram. The PRISMA checklist should be submitted as a separate file along with the manuscript. For information regarding PRISMA guidelines, please visit http://www.prisma-statement.org or EQUATOR Network (https://www.equator-network.org/home/). Systematic reviews and meta-analyses of observational studies in epidemiology should be reported according to MOOSE guidelines. For more information regarding MOOSE guidelines, please visit http://www.equator-network.org/reporting-guidelines/meta-analysis-of-observational-studies-in-epidemiology-a-proposal-for-reporting-meta-analysis-of-observational-studies-in-epidemiology-moose-group/.

· No limitation the number of the references.

3) Case Reports

A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or population, that is so unusual that a clinical trial is not feasible.

Case reports of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Rarity of a disease condition is itself not an acceptable justification for a case report.

(1) Title page: Same as clinical and experimental studies.

(2) Manuscript

① Title and Running title.

② Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicomma (;), and mark a period (.) at the end of the last word.

③ Introduction: Should not be separately divided. Briefly describe the case and background without a title.

④ Case report: Describe only the clinical statement that is directly related to diagnosis and anesthetic management.

⑤ Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.

⑥ References: Do not exceed 15 references. For exceeding the number of references, it should be negotiated with the Editorial Board.

⑦ Tables and figures: Proportional to clinical and experimental studies.

4) Reviews

Review articles synthesize previously published material into an integrated presentation of our current understanding of a topic. Review articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review articles should include unstructured abstracts equal to or less than 250 words in English. Figures and tables should be provided in English. References should be obviously related to documents and should not be exceed 100. For exceeding the number of references, it should be negotiated with the Editorial Board. Body text should not exceed 30 A4 pages, and the number of figures and tables should be equal to or less than 6.

5) Letters to the Editor

Letters to the Editor also should include brief constructive comments on the articles published in KJA and interesting cases. Book reviews as well as news of scientific societies and scientific meeting dates in Korea or abroad can be included. Letters to the editor of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Letters to the Editor cover individual articles not described by any of the above categories. The short manuscripts with a constructive note on the Journal or the anesthesiology at large are welcome.

Cover pages should be formatted as those of clinical research papers. The body text should not exceed 1,000 words and should have no more than 5 references. For exceeding the number of references, it should be negotiated with the Editorial Board. A figure or a table may be used. A maximum of five au-

thors is allowable. Letter may be edited by the Editorial Board and if necessary, responses of the author of the subject paper may be provided.

6) Statistical Round

A Statistical Round is a narrative review of the application of contemporary quantitative sciences to issues of concern to anesthesia researchers. A Statistical Round involves a focused discussion on one or more unique or interesting statistical analysis methods that has previously been published in this journal or expresses the general policies or opinions of the Statistical Round Board. They are solicited by the Statistical Round Board and reviewed by the Statistical Editor. There are no word limits to or rules regarding the structure of a Statistical Round. They should have an unstructured abstract of no more than 250 words in English. All articles in a Statistical Round will be published in English and translated into Korean for the convenience of Korean readers. The Korean version of the Statistical Round will be published only on the Web page of the Journal (https://ekja.org). The inclusion of sample datasets as Web (Supplemental) content is encouraged.

8. Recently revised instructions for authors are applied from December 2023 submissions.